FINAL REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Systematic review to examine the clinical effectiveness and tolerability of chemotherapy for older people with non-Hodgkin's lymphoma

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Title: Systematic review to examine the clinical effectiveness and tolerability of chemotherapy for older people with non-Hodgkin's lymphoma

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Abbreviations:

A-CHOP	Amifostine plus cyclophosphamide, doxorubicin, vincristine and prednisone
ADL	Activities of Daily Living
AE	Adverse event
CEMP	Cisplatinum, etoposide, mitoxantrone and prednisone
CEOP	Cyclophosphamide, vincristine, epirubicin and prednisone
CEOP/IMVP-Dexa	Cyclophosphamide, epirubicin, vincristine, prednisolone, ifosfamide, uromitexan, VP-16, dexamethasone, methotrexate and Ca folinate
CGA	Comprehensive geriatric assessment
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CHOP plus G-CSF	Cyclophosphamide, doxorubicin, vincristine, and prednisone plus granulocyte colony-stimulating factor
CHVP	Cyclophosphamide, doxorubicin, vindesine and prednisone
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CMD	Irinotecan, mitoxantrone and dexamethasone
COPBLAM-V	Cyclophosphamide, vincristine, bleomycin, doxorubicin, procarbazine and prednisone
CR	Complete response
CyclOBEAP	Doxorubicin, cyclophospamide or etoposide, vincristine, prednisone, with or without bleomycin
DA-POCH-R	Dose-adjusted infusional cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy with rituximab
DLBCL	Diffuse large B-cell lymphoma
DFS	Disease-free survival
DRCOP	R-CHOP with pegylated liposomal doxorubicin
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMP	Etoposide, mitoxantrone and prednisone
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC quality of life cancer questionnaire
ESHAP	Etoposide, cisplatin, solumedrol and aracytine
EPOCH	Eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone
FACT-G	Functional Assessment of Cancer Therapy-General
F-CVP	Fludarabine phosphate, cyclophosphamide, vincristine and prednisone
FFS	Failure-free survival
FL	Follicular lymphoma
FLIPI	Follicular lymphoma International Prognostic Index
FM	Fludarabine and mitoxantrone
G-CSF	Granulocyte colony-stimulating factor
GPD	Gemcitabine, cisplatin and dexamethasone
HR	Hazard ratio
IADL	Instrumental Activities of Daily Living
IFN	Interferon

IPI	International Prognostic Index
ITT	Intention to treat
KPS	Karnofsky Performance Status
LDH	Lactate dehydrogenase
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MCOP	Cyclophosphamide, mitozantrone, vincristine and prednisolone
MEMID	Mitoxantrone, VP16, methylglyoxal, ifosfamide and dexamethasone
Mini-CEOP	Cyclophosphamide, epidoxorubicin, vinblastine and prednisone
Mini-CHVP	Cyclophosphamide, doxorubicin, vindesine and prednisone
Mini-FLEC	Low-dose fludarabine, epirubicin, prednisone and cyclophosphamide
MMS	Mini-mental status
NAEPP plus G-CSF	Vinorebine, epirubicin and prednisone plus granulocyte colony-stimulating factor
NCEI	National Cancer Equity Initiative
NHL	Non-Hodgkin's lymphoma
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PAdriaCEBO	Prednisolone, adriamycin, cyclophosphamide, etoposide, vincristine and bleomycin
PCNSL	Primary central nervous system lymphoma
PFS	Progression-free survival
PMitCEBO	Prednisolone, mitoxantrone, cyclophosphamide, etoposide, vincristine and bleomycin
POI	Pharmaceutical Oncology Initiative
PS	Performance status
PTCL	Peripheral T-cell lymphoma
P-VEBEC	Epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin and prednisone
PWB	Physical well-being
QoL	Quality of life
RR	Response rate
R-BM	Mitoxantrone and bendamustine plus rituximab
R-CEOP	Cyclophosphamide, vincristine and epirubicin, prednisone, plus rituximab
R-CVP	Cyclophosphamide, vincristine and prednisone plus rituximab
R-CVEP	Cyclophosphamide, etoposide, prednisone, procarbazine and vorinostat plus rituximab
R-CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab
R-CNOP	Cyclophosphamide, mitoxantrone, vincristine and prednisone plus rituximab
RCT	Randomised controlled trial
RDI	Relative dose intensity
R-FC	Rituximab, fludarabine and cyclophosphamide
R-FND	Rituximab, fludarabine, mitoxantrone, dexamethasone
R-GemOx	Gemcitabine and oxaliplatin plus rituximab

R-mini-CEOP	Epirubicin, cyclophosphamide, vinblastine and prednisone plus rituximab
R-mini-CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab
R-THP-COP	Tetrahydropyranyl adriamycin–cyclophosphamide, vincristine and prednisolone plus rituximab
R-VNCOP-B	Etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, bleomycin and rituximab
SD	Standard deviation
SLL	Small lymphocytic lymphoma
THP-COP	Tetrahydropyranyl adriamycin–cyclophosphamide, vincristine and prednisolone
THP-COP plus G-CSF	Tetrahydropyranyl adriamycin–cyclophosphamide, vincristine and prednisolone plus granulocyte colony stimulating factor
THP-COPE	Tetrahydropyranyl adriamycin–cyclophosphamide, vincristine and prednisolone plus etoposide
TTF	Time to treatment failure
TTR	Time to relapse
TTP	Time to disease progression
VNCOP-B	Cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin and prednisone
VNCOP-B plus G-CSF	Cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin and prednisone plus granulocyte colony-stimulating factor
WHO	World Health Organisation

Definition of terms:

Biological therapy	Treatments that use natural substances from the body, or drugs made from these substances, to fight cancer or to lessen the side-effects that may be caused by some cancer treatments. An example includes trastuzumab (Herceptin)
Chemotherapy	The treatment of cancer with cytotoxic anticancer drugs
Heterogeneity	In statistics this means that there is between-study variation. If heterogeneity exists, the pooled effect size in a meta-analysis has no meaning as the presence of heterogeneity indicates that there is more than one true effect size in the studies being combined

1 EXECUTIVE SUMMARY

1.1 Background

Older people with cancer are less likely to receive radical treatment for their disease, due to comorbidities and/or frailty associated with old age, and uncertainty over the tolerability of chemotherapy treatment in older patients. The National Cancer Equity Initiative (NCEI) is focussed on reducing cancer inequalities, which includes improving outcomes for older patients with cancer. In collaboration with the Pharmaceutical Oncology Initiative (POI), the NCEI is seeking to deepen the understanding of current practice in relation to cancer treatment for older people, with the aim of enabling a more personalised treatment protocol, which takes into account fitness, choice and benefit to the individual.

1.2 Aims and objectives

The aim of this review is to systematically review the evidence for the clinical effectiveness and tolerability of chemotherapy used to treat non-Hodgkin's lymphoma (NHL) in older people.

1.3 Methods

Search strategy

Four electronic databases (MEDLINE, EMBASE, The Cochrane Library and Web Of Knowledge) were searched from January 2000 to May 2013.

Study selection

The references identified were assessed for inclusion through two stages. In stage 1, two reviewers independently screened all relevant titles and abstracts identified via electronic searching and selected potentially relevant studies for inclusion in the review. In stage 2, full-text copies of the potentially relevant studies were obtained and assessed independently by two reviewers. Any disagreements between reviewers were resolved by discussion with a third reviewer at each stage. Studies that did not meet the inclusion criteria were excluded.

Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in an Excel spreadsheet using a sample of included studies, and adapted to reflect the nature of both randomised controlled trials and observational studies. Data were extracted on study design, population characteristics and outcomes by one reviewer and independently checked for accuracy by a second reviewer, with disagreements resolved through discussion with a third reviewer where necessary.

Evidence synthesis

Due to the heterogeneity of the included studies and the limited data available, it was not possible or appropriate to perform any statistical analyses. The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary.

1.4 Results

Electronic searching of databases resulted in 823 references. Manual de-duplication of references resulted in 736 unique references for screening at stage 1.

Initial screening of titles and abstracts identified 415 references, which were obtained as full-text papers. A total of 129 references (108 studies) met the inclusion criteria at stage 2 and were included in the review. The 108 studies included in the review were divided into six categories, based on study design.

1.5 Conclusions

There is much research into the treatment of 'older' or 'elderly' people with NHL, but it is generally of poor quality. There is a lack of consistency in NHL trials, such as differences in the definition of 'older' or 'elderly', and in the use and reporting of standard assessment measures for outcomes, such as efficacy and tolerability. Few data are collected for quality of life and comprehensive geriatric assessments.

Chemotherapy can benefit fit older patients, but there is a risk of increased toxicity for many regimens used to treat aggressive NHL. Older patients should therefore have an opportunity to discuss treatment options with healthcare professionals. Even though age is a risk factor for toxicity, age alone should not be a barrier to chemotherapy for patients with NHL, as other factors including fitness, comorbidities and personal choice should be taken into account.

2 BACKGROUND

Older people with cancer are less likely to receive radical treatment. There are a number of reasons for this, including comorbidities and/or frailty associated with older age, and a complex mix of factors affecting patient and/or clinician choice. There is also uncertainty about the tolerability of chemotherapy treatment in older patients. However, not all older people are frail; many have good life expectancy and are in good health overall. There is evidence to suggest that characteristics other than age are not always fully assessed by healthcare professionals when treating older people with cancer, some of whom may be able to tolerate effective treatment.

The National Cancer Equity Initiative (NCEI) is focussed on reducing cancer inequalities, which includes improving outcomes for older patients with cancer. In collaboration with the Pharmaceutical Oncology Initiative (POI), the NCEI is seeking to deepen the understanding of current practice in relation to cancer treatment for older people, with the aim of enabling a more personalised treatment protocol, which take into account fitness, choice and benefit to the individual.

Older patients are underrepresented in clinical trials, and study results are not generally applicable to the older population typically seen in routine clinical practice due to the enrolment of fitter and healthier patients. As a result, there are limited data on the efficacy and tolerability of chemotherapy for this patient population.

2.1 Description of health problem

Non-Hodgkin's lymphoma (NHL) is the sixth most common cancer in the UK, with 12,900 new cases in the UK in 2012.[1] Non-Hodgkin's lymphoma is a group of over 60 heterogeneous, lymphoproliferative malignancies, with characteristics and treatment responses that depend on histological type, stage of disease and treatment choice.[2,3] Non-Hodgkin's lymphoma has a tendency to spread to extranodal sites; this dissemination correlates to the stage of the disease.[3] There are two categorisations of NHL, either indolent (slow-growing lymphoma) or an aggressive, fast-growing lymphoma. The type of white blood cell involved and whether it is follicular or diffuse are also considered.[4] The two most common subtypes of NHL are diffuse large B-cell lymphoma (DLBCL), which is aggressive, and follicular lymphoma, which is indolent. For all types of NHL in the UK, mortality rates are highest in people over the age of 85 years, with 54% of deaths occurring in people aged 75 years and over between 2010 and 2012.[1]

2.2 Aetiology

There are many risk factors for NHL depending on the histology of the disease. These include compromised immune system, infection and age.[5,6] The incidence of NHL, within all subgroups, increases greatly with age. In the UK between 2009 and 2011, 86% of diagnoses occurred in those aged over 50, with 34% of all occurrences being in men and women aged 75 and over. There is a

steep increase in age-specific occurrences from age 50-54 peaking at around 80-84 years. In Great Britain, records of NHL have increased three-fold since the mid-1970s.[7]

2.2.1 Pathology and prognosis

Pathology and prognosis of NHL are dependent on a range of factors. Clinicians use the International Prognostic Index (IPI) to determine the outlook for a patient. The factors that are taken into consideration for IPI are age, stage, performance status (PS), spread to extranodal sites and serum level of lactate dehydrogenase (LDH).[8] There are other variants of the IPI, including the revised IPI, age-adjusted IPI and follicular lymphoma IPI (FLIPI), which adjust the outcome according to relevant factors.

When considering all subtypes of NHL, the age-standardised relative 5-year survival rate between 2010-2011 was 69%.[9] As discussed, prognosis can vary dramatically when taking into account different factors, including type of NHL, stage at diagnosis and age. For people aged 50-59 years, the 5-year survival rates were 74% and 81% for men and women, respectively, whereas for people aged 70-79 years, survival rates were 53% and 61%.[10]

2.3 Current treatment options

There are many treatment options for NHL, depending on the nature of the disease (aggressive or indolent) and the specific subtype of lymphoma.

Indolent lymphomas

Immediate treatment for indolent lymphomas is not often required as they are slow to develop and may be asymptomatic. Although they generally require low-dose treatment, they can be very difficult to eradicate.[11] The treatment options for follicular lymphoma (FL) include 'watch and wait', radiotherapy, immunotherapy, chemotherapy for more advanced FL and rituximab for maintenance therapy.[12]

Aggressive lymphomas

Chemotherapy is the standard first-line treatment for aggressive lymphomas. For patients in whom initial chemotherapy has failed or who have relapsed, autologous stem cell transplant may be performed with or without additional chemotherapy. For aggressive lymphomas, such as DLBCL, treatment has positive outcomes for the majority of patients even though the disease is fast growing.[11]

3 AIMS AND OBJECTIVES

3.1 Objectives

The aim of this review is to systematically review the evidence for the clinical effectiveness and tolerability of chemotherapy regimens used to treat NHL in older people. The review forms part of a larger project, which focusses on six types of cancer in older populations: breast, colorectal, lung, renal cell, chronic myeloid leukaemia and non-Hodgkin's lymphoma. The final report will consist of the results of a systematic review of the literature in each of these six clinical areas.

The objectives of this review are to:

- systematically review and summarise the relevant evidence relating to clinical effectiveness and tolerability of treatment
- explore the implications of these findings for practice and service provision in order to disseminate accessible information to clinicians
- inform future decisions on research priorities through the identification of gaps and weaknesses in the available evidence.

3.2 Inclusion considerations

The population of interest is older people with NHL. There is no agreed definition of 'older': the World Health Organisation[13] states that most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly' or 'older,' whereas the British Geriatrics Society[14] describes geriatric medicine as being mainly concerned with people aged over 75. We have therefore focussed on published studies that specifically describe their patients or subgroups of patients, as 'older' or 'elderly'. In order to obtain a comprehensive dataset, no restrictions have been made with regard to the stage of disease, tumour histology or the line of treatment described in the literature.

All forms of chemotherapy (defined as a systemic anti-cancer therapy) commonly used for NHL have been considered. To ensure that the most recent treatments are included it was decided, in consultation with clinical experts, that targeted biological therapies would also be considered, based on the premise that the two treatment types tend to be considered equally efficacious in clinical practice.

4 METHODS

4.1 Search strategy

Four electronic databases (MEDLINE, EMBASE, The Cochrane Library and Web Of Knowledge) were searched from January 2000 to May 2013, and all references were exported to EndNote® version X4. A comprehensive search strategy was employed and is included in Appendix 1.

4.2 Study selection

The references identified were assessed for inclusion through two stages. In stage 1, two reviewers independently screened all relevant titles and abstracts identified via electronic searching and selected potentially relevant studies for inclusion in the review. In stage 2, full-text copies of the potentially relevant studies were obtained and assessed independently by two reviewers using the inclusion criteria outlined in **Error! Not a valid bookmark self-reference.**. Any disagreements between reviewers were resolved by discussion with a third reviewer at each stage. Studies that did not meet the inclusion criteria at stage 2 were excluded.

Table 1 Inclusion criteria

Study design	Randomised controlled trials; systematic reviews; cohort studies, including retrospective studies of databases and registries
Patient population	Older people (older as defined by study authors) treated for NHL
Interventions	Any chemotherapy (all lines of treatment)
Comparators	• an alternative chemotherapy or • best supportive care
Outcomes	Efficacy outcomes • overall survival or • progression-free survival • response rates Tolerability outcomes • adverse events • tolerability Other outcomes • quality of life measures • comprehensive geriatric assessment
Other considerations	Papers that reported subgroup analyses of older people in their abstract were included Only studies published since 2000 in full or with an English language abstract were included

NHL=non-Hodgkin's lymphoma

4.2.1 Outcomes

The majority of outcomes presented in this review are commonly used measures of survival or response to treatment; however, 'tolerability' and 'comprehensive geriatric assessment (CGA)' may require further explanation.

Tolerability

In order to determine whether or not older patients can tolerate chemotherapy treatment, it was necessary to gather evidence from a range of outcomes. One measure of tolerability is a patient's

adherence to the treatment regimen and/or how much of the treatment was received. Common measures reported in studies are the mean or median number of cycles delivered per patient, how many people completed the treatment and the relative dose intensity (RDI) of treatment. Therefore, data were extracted from any measure that could be used to determine how much treatment a patient received.

Treatment discontinuations and withdrawals are other measures of how well a patient has tolerated chemotherapy. Therefore, any data relating to discontinuation due to toxicity, withdrawal of consent, disease progression or death were extracted.

Many studies report the number of patients whose dose of treatment was modified or interrupted due to adverse events (AEs), which again is a good measure of how well a treatment is tolerated. Any data that encompassed modifications or interruptions in treatment were extracted.

Randomised controlled trials (RCTs) commonly report AEs, and therefore all reported AEs of grade 3 or higher that occurred in more than 10% of patients in each arm were included in data extraction, together with any information on toxic deaths.

Geriatric assessment

Comprehensive geriatric assessment is often carried out to determine an older person's health, both physical and mental, in order to decide on the appropriate treatment pathway for the individual. There are numerous tools used by clinicians, and studies often use CGA to determine eligibility for trials or as an outcome measure to establish how well the patient has responded to treatment in terms of how fit and well they are.

4.3 Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in an Excel spreadsheet using a sample of included studies, and then adapted to reflect the nature of both RCTs and non-randomised studies. Data were extracted on study design, population characteristics and outcomes by one reviewer and independently checked for accuracy by a second reviewer, with disagreements resolved through discussion with a third reviewer where necessary.

Included RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance.[15] Data relating to quality assessment were extracted by one reviewer and independently checked for accuracy by a second reviewer. Where necessary, disagreements between reviewers were discussed in consultation with a third reviewer to achieve consensus. Full details of quality assessment criteria are provided in Appendix 2.

No universally accepted standardised quality assessment tool exists for use in non-randomised studies. There are a multitude of non-randomised study designs, and so even where tools exist, applying them is problematic and of limited value. Due to the nature of the study designs of the included non-randomised studies, it was difficult to extract or compare information in a meaningful and relevant manner. Therefore, we made the pragmatic decision not to quality assess the non-randomised studies.

4.4 Evidence synthesis

Due to the heterogeneity of the included studies and insufficient data, it was not possible or appropriate to perform any statistical analyses. The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary.

5 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

5.1 Number of studies identified

Electronic searching of databases resulted in the identification of 823 potentially relevant references. After manually de-duplicating references, there were 736 unique references available for screening at stage 1. Details are summarised in Figure 1.

Initial screening identified 415 references to obtain as full-text papers, to which inclusion criteria were applied (stage 1). A total of 108 studies (reported in 129 references) were included at stage 2. A list of references excluded at stage 2 is presented in Appendix 3. The 108 studies included in the review were divided into categories based on study design. Table 2 presents the number of studies in each category and a brief description of the study type.

Table 2 Categorisation of included studies

Study type	Definition	Number of studies
RCTs	RCTs recruiting only patients defined as elderly/older	18
Subgroup analyses of RCTs	Analyses of RCTs from the general population with elderly/older subgroups reported separately	0
Pooled analyses	Published studies that use aggregated subgroup data on elderly/older patients from RCTs	1
Prospective comparative cohorts	Studies that report two or more comparators of a non-randomised trial with an elderly/older population	4
Prospective single cohorts	Studies that report single cohorts of elderly/older patients	63
Retrospective data	Any reports of chemotherapy treatment for elderly/older patients in a defined cohort of patients or from registries of patient outcomes	22
Total		**108**

RCT=randomised controlled trial

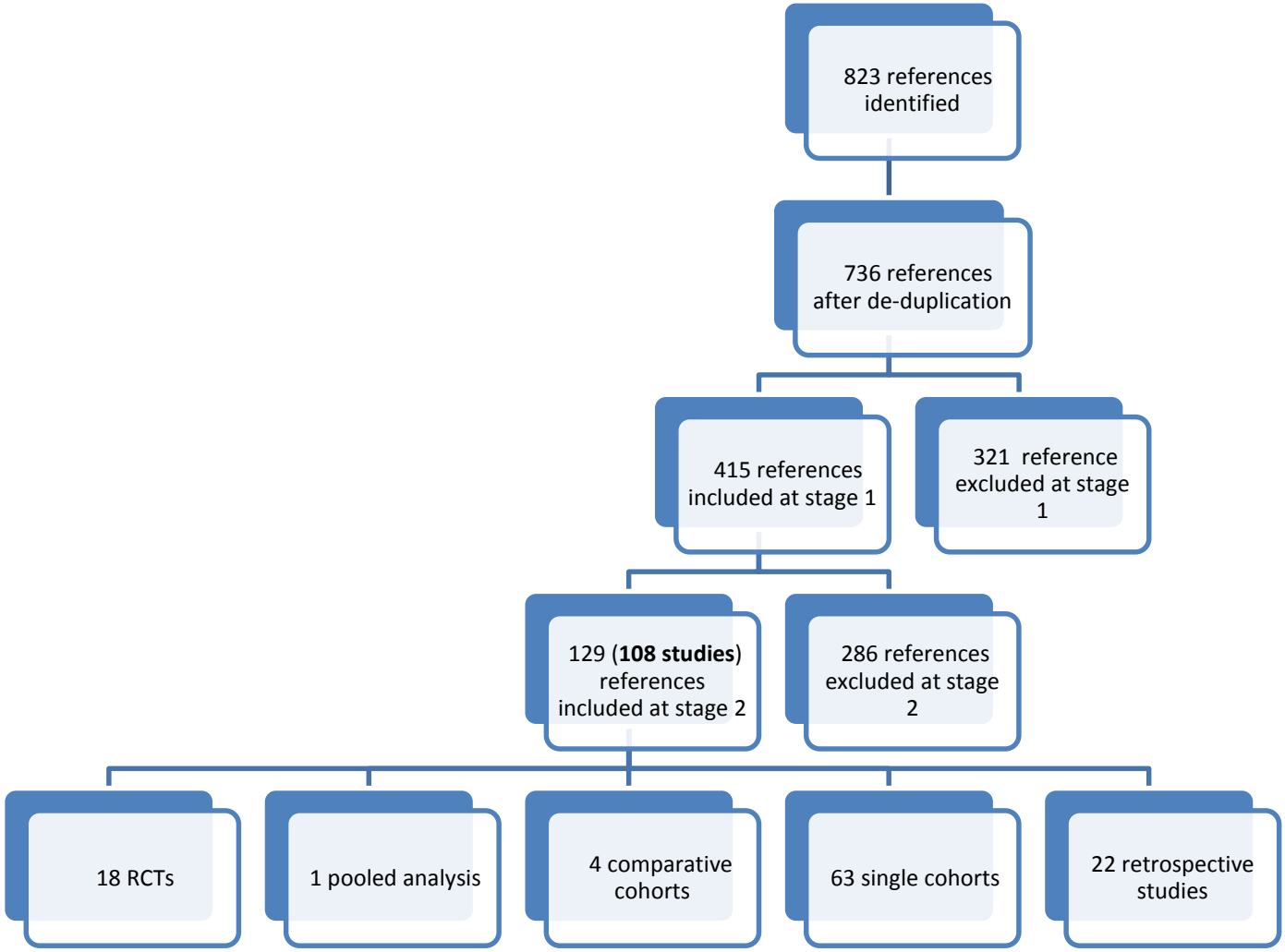

Figure 1: Flow diagram of included studies

6 RANDOMISED CONTROLLED TRIALS

A total of 18 RCTs (reported in 32 publications[16-47]) met the inclusion criteria and were included in the review. The majority of trials focussed on populations of patients with aggressive types of NHL; however, one trial[31] focussed on patients with indolent disease, and in two trials,[32,33] the patient population was mixed or unclear.

6.1 Quality assessment of randomised controlled trials

Quality assessment of the included RCTs is presented in Table 3. Seventeen RCTs[16-24,26-33] were included in the quality assessment exercise; one RCT[25] was reported in abstract format only and did not provide sufficient information to be assessed for methodological quality.

Seven of the included trials[16,18,20,21,23,30,32] were assessed as being truly random; however, only three[21,23,30] presented sufficient information to be assessed as having adequately concealed patient randomisation. All trials reported the number of patients randomised and patient baseline data. Baseline comparability of patients was achieved in all trials. Four trials[16,17,31,32] were reported as open label; the blinding protocols in the remaining trials were unclear.

All trials, with the exception of Delarue et al,[16] reported that >80% of patients were included in the final analyses. With the exception of Aribi et al,[20] all trials reported the reasons for patient withdrawals. An intention-to-treat (ITT) analysis was not performed in six trials,[20,23,24,27,29,30] and three trials[20,26,33] did not provide information relating to calculations for the statistical powering of the trial. All trials appeared to report the results of all of the outcomes they set out to measure.

Table 3 Quality assessment, randomised controlled trials

Study	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		Other measures	ITT	Powering
	Truly random	Allocation concealment	Number stated	Baseline presented	Baseline achieved			Assessors	Administrators	Participants	Procedure assessed	>80% in final analysis	Reasons stated			
Delarue 2013[16]	✓	X	✓	✓	✓	✓	✓	N/A	N/A	N/A	N/A	X	✓	X	✓	✓
Gomez 2013[17]	X	?	✓	✓	✓/X	✓	X	NA	NA	NA	NA	✓	NA	X	✓	✓
Kluin-Nelemans 2012[18]	✓	?	✓	✓	✓	✓	X	?	?	?	?	✓	✓	X	✓	✓
Merli 2012[19]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	✓	✓
Aribi 2010[20]	✓	X	✓	✓	✓	✓	X	?	?	✓	?	✓	X	X	X	X
Coiffier 2010[21]	✓	✓	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	✓	✓
Aviles 2007[22]	?	X	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	✓	✓
Balducci 2007[32]	✓	?	✓	✓	✓	✓	✓	N/A	N/A	N/A	N/A	✓	✓	X	✓	✓
Merli 2007[23]	✓	✓	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	X	✓
Habermann 2006[24]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	X	✓
Chamorey 2005[26]	?	?	✓	✓	?	✓	X	?	?	?	?	✓	✓	X	✓	X
Foussard 2005[31]	?	?	✓	✓	✓	✓	✓	N/A	N/A	N/A	N/A	✓	✓	X	✓	✓
Mori 2005[33]	?	?	✓	✓	✓	✓	X	?	?	?	?	✓	✓	X	✓	X
Bessell 2003[27]	X	X	✓	✓	✓	✓	X	?	?	?	?	✓	✓	X	X	✓
Doorduijn 2003[28]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	✓	✓
Zinzani 2002[29]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	X	✓
Mainwaring 2001[30]	✓	✓	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	X	X	✓

Items graded in terms of ✓ yes (item properly addressed), ✕ no (item not properly addressed), ✓/✕ partially (item partially addressed), ? Unclear/not enough information, or N/A not applicable

6.2 Study characteristics

Study characteristics for the 18 included RCTs[16-33] are presented in Table 4. The RCTs are categorised according to the type of NHL (i.e. aggressive, indolent or mixed/unclear).

6.2.1 Aggressive disease

Fifteen trials[16-30] addressed an aggressive form of NHL. Nine trials[16,21,23-28,30] were described as phase III trials, one RCT[17] was a phase II trial, and five trials[18-20,22,29] did not state the phase. Funding for one trial[27] was provided by a pharmaceutical company, three trials[19,23,28] were funded by research grants and four trials[16,18,21,24] were jointly funded by pharmaceutical companies and research grants. Seven trials[17,20,22,25,26,29,30] did not report funding. Eleven trials[16,18,19,21,23,25-30] were conducted across a number of European countries (Bessell et al[27] and Mainwaring et al[30] were UK-based), two trials[17,22] were conducted in South America, one in North America and Canada[24] and one in Algeria.[20]

The included trials recruited relatively small numbers of patients. Two trials[17,20] recruited fewer than 100 patients, seven trials[19,22,23,25-27,29] recruited between 100 and 300 patients, and six trials[16,18,21,24,28,30] recruited more than 300 patients. Mainwaring et al[30] was the largest trial with 669 patients. The majority of patients in each of the trials had stage III or stage IV disease. The exceptions were the Gomez et al[17] and Aribi et al[20] (equal mix of stages I, II, III and IV), and Bessell et al[27] (majority stage I or stage II).

The definition of older (minimum age for trial eligibility) was set at 60 years for seven trials[16,18,20,21,24,29,30] and 65 years for seven trials.[19,22,23,25-28] The minimum age for recruitment to Gomez et al was 69 years.[17] The median age of participants ranged from 69[21] to 74.[17,23,27] Aribi et al[20] reported a mean patient age of 66 years. Where reported, the majority of patients recruited to the trials had a PS of 0 or 1. Aviles et al[22] reported that 45% of patients had a PS of 2 or 3. Eight trials[16,19-24,30] included only patients with DLBCL, and Kluin-Nelemans et al[18] included only patients with mantle-cell lymphoma. Six trials[17,25-28] included a mix of disease types. With the exception of Aribi et al,[20] all patients were previously untreated, and the line of treatment was unclear in Gomez et al.[17]

A range of treatments were administered across the trials, the most frequent were cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Other treatments included amifostine plus CHOP (A-CHOP); CHOP plus granulocyte colony-stimulating factor (G-CSF); cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin and prednisone (VINCOP-B); VINCOP-B plus G-CSF, rituximab, fludarabine, and cyclophosphamide (R-FC); cyclophosphamide, vincristine, epirubicin and prednisone (CEOP); rituximab, epirubicin, cyclophosphamide, vinblastine and prednisone (R-CEOP); etoposide, cisplatin, solumedrol, aracytine (ESHAP); gemcitabine, cisplatin, dexamethasone (GPD); epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin and prednisone (P-VEBEC); mitoxantrone,

VP16, methylglyoxal, ifosfamide and dexamethasone (MEMID); cyclophosphamide, mitozantrone, vincristine, prednisolone (MCOP); prednisolone, adriamycin, cyclophosphamide, etoposide, vincristine, and bleomycin (PAdriaCEBO); and prednisolone, mitoxantrone, cyclophosphamide, etoposide, vincristine, and bleomycin (PMitCEBO).

6.2.2 Indolent disease

Only one included trial[31] focussed on indolent disease. Foussard et al[31] was a phase III multicentre trial based in France and funded by a pharmaceutical company. The 144 recruited patients had previously untreated, advanced follicular and non-follicular lymphoma and 17% had a PS of >1. The majority (96%) of patients had stage III or stage IV disease. The median age of the recruited patients was 66 years. The treatments administered were cyclophosphamide, doxorubicin, vindesine, prednisone (CHVP) and fludarabine plus mitoxantrone (FM).

6.2.3 Mixed or undefined disease

Two trials were categorised as having a mixed or unclear patient population: Balducci et al[32] and Mori et al.[33] The patients (n=146) recruited to the phase IV Balducci et al trial[32] were described as having NHL and were randomised to a trial that also included patients with lung, breast or ovarian cancers. The patients (n=443) recruited to the phase III Mori et al trial[33] were described as having a range of NHL subtypes. Balducci et al[32] was based in North America and Mori et al[33] was based in Japan. Balducci et al[32] reported that funding was provided by a pharmaceutical company, whereas no funding source was reported by Mori et al.[33]

All patients recruited were previously untreated and the majority had a PS of 0 or 1; however, 31% of patients in Mori et al[33] had a PS of 2 to 3. The median age of patients was 72 years in Balducci et al[32] and 74 years in Mori et al.[33] The greatest proportion of patients recruited to the trials had stage III or stage IV disease.

The treatment regimen in Balducci et al[32] was CHOP, R-CHOP or eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone (EPOCH), with or without pegfilgrastim. Patients recruited to Mori et al[33] were treated with tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone (THP-COP), CHOP or tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone plus etoposide (THP-COPE).

Table 4 Study characteristics, randomised controlled trials

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
NHL – Aggressive disease						
Delarue 2013[16]	Phase III Multicentre France, Belgium, Switzerland and Portugal Follow-up 56 months (27-60) 2003-2008 Funding: GELA and Agmen	DLBCL R-CHOP-14: 86% R-CHOP-21: 85% First-line ≥60 years Stage: I-II=12% III-IV=88%	R-CHOP-14 (every 14 days) (n=304)	Median age: 70 years (60-80) Male: 56% ECOG PS: 0-1=81%; ≥2=19%	Primary endpoint: EFS Secondary endpoints: ORR, PFS, DFS, OS and toxicity	In elderly patients with untreated DLBCL and at least one adverse prognostic factor, a 2-week dose-dense R-CHOP regimen did not improve efficacy compared with the 3-week standard schedule. The frequency of toxic side-effects was similar between regimens, but R-CHOP14 was associated with increased need for red-blood-cell transfusion
			R-CHOP-21 (every 21 days) (n=298)	Median age: 70 years (59-80) Male: 55% ECOG PS: 0-1=74%; ≥2=26%		
Gomez 2013[17]	Phase IIb 2 centres Peru Follow-up 8 years Funding: NR	DLBCL Peripheral T-cell MCL MALT (high grade) Follicular grade III Unclassifiable Treatment line unclear >69 years Stage: I-II=57% III-IV=43%	A-CHOP (n=18)	Median age: 74 years (70 to 83) Male: 39% ECOG PS: NR	TTP, DFS, OS and toxicity	These results show that amifostine can be added to the standard CHOP treatment schedule with less acute toxicity and without influencing the outcome
			CHOP (n=16)	Median age: 73 years (70 to 84) Male: 44% ECOG PS: NR		
Kluin-Nelemans 2012[18]	Phase NR Multicentre Europe Follow-up induction 37 months, maintenance 36 months 2004-2010 Funding: European Commission, Lymphoma Research Foundation, Roche Pharmaceuticals, Bayer Schering Pharma and Schering-Plough	MCL First-line ≥60 years Stage: II=6% III/IV=93%	R-CHOP (n=280) or R-FC (n=280) followed by maintenance rituximab (n=155) or IFN (n=161)	Median age: 70 years (60-87) Male: 70% ECOG PS 0 to 2	Primary endpoints: Induction=CR Maintenance=duration of remission Secondary endpoints: ORR, TTF, OS and toxicity	R-CHOP induction followed by maintenance therapy with rituximab is effective for older patients with MCL

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Merli 2012[19]	Phase NR Multicentre Italy Follow-up 42 months (5-81) 2003-2006 Funding: Associazione Angela Serra per la Ricerca sul Cancro, and GR.A.D.E.	DLBCL First-line >65 years Stage: II=31% III-IV=69%	R-CHOP (n=110)	Median age: 71 years (65-86) Male: 50% ECOG PS: 0-1=91%; ≥2=9%	Primary endpoint: EFS Secondary endpoints: ORR, OS, RFS and toxicity	Patients older than 72 years and with low-risk disease had a better outcome when treated with R-mini-CEOP (p=0.011). Overall R-CHOP and R-mini-CEOP are similarly effective for elderly 'fit' patients with DLBCL. The less intense R-mini-CEOP may be an acceptable option for the treatment of relatively older patients with low-risk disease
			R-mini-CEOP (n=114)	Median age: 73 years (64-84) Male: 43% ECOG PS: 0-1=84%; ≥2=16%		
Aribi 2010[20]	Phase NR Single centre Algeria 2005-2008 Funding: NR	DLBCL Relapsed/refractory to CHOP ≥60 years Stage: I/II=50% III/IV=50%	ESHAP (n=48)	Mean age: 66.2±2.5 years Male: 56% ECOG PS: >1=17%	Primary endpoint: OS, PFS, EFS	In cases of contraindication for high-dose chemotherapy for elderly patients with DLBCL, without complete remission, the gemcitabine-based therapy protocol represents a more effective and less toxic regimen than that of ESHAP
			GPD (n=48)	Mean age: 65.4±3.6 years Male: 50% ECOG PS: >1=15%		
Coiffier 2010[21]	Phase III Multicentre France, Belgium Follow-up 10 years 1998-2000 Funding: F. Hoffmann-La Roche, GELA, Genetech	DLBCL First-line ≥60 Stage: I/II=21% III/IV=79%	R-CHOP (n=202)	Median age: 69 years (60-80) Male: 46% ECOG PS: 0=22%; 1=45%; >1=22%	Primary endpoint: EFS Secondary endpoints: OS, PFS, DFS, ORR and toxicity	The results from the 10-year analysis confirm the benefits and tolerability of the addition of rituximab to CHOP. Our findings underscore the need to treat elderly patients as young patients, with the use of curative chemotherapy
			CHOP (n=197)	Median age: 69 years (60-80) Male: 54% ECOGPS: 0=17%; 1=48%; >1=17%		
Aviles 2007[22]	Phase NR Single centre Mexico Follow-up 58.6 months (24-84) 1999-2003	DLBCL First-line >65 Stage: III/IV=100%	Escalated CEOP (n=103)	Median age: 69.6 years (65-83) Male: 57% ECOG PS: 0=17%; 1=34%; 2=28%; 3=19%	Primary endpoint: EFS Secondary endpoints: OS and frequency of toxic effects	In elderly patients with DLBCL and poor prognostic factors, rituximab did not improve their outcome

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Funding: NR		Escalated R-CEOP (n=101)	Median age: 68.9 years (65-85) Male: 47% ECOG PS: 0=28%; 1=26%; 2=20%; 3=22%		
Merli 2007[23]	Phase III Multicentre Italy 72 months (9 to104) 1996-1999 Funding: partially supported by GRADE (Gruppo Amici dell'Ematologia), Reggio Emilia, and Associazione Angela Serra per la Ricerca sul Cancro	DLBCL First-line >65 Stage: III-IV=73%	Mini-CEOP [6 cycles] (n=125)	Median age: 73 years (66-87) Male: 38% ECOG PS: 2 to 4=27%	Survival, response and QoL	Both mini-CEOP and P-VEBEC determined a similar outcome for elderly patients with DLBCL, with a third of patients alive after more than 6 years of follow-up. Both regimens can be considered equally for combination treatment with anti-CD20 monoclonal antibody therapy
			P-VEBEC [8 cycles] (n=107)	Median age: 74 years (65-86) Male: 44% ECOG PS: 2 to 4=30%		
Haberman 2006[24]	Phase III Multicentre US & Canada 42 months 1998-2001 Funding: Pfizer, Berlex, Genetech, Roche, Biogen, National Cancer Institute, National Institutes of Health and The Department of Health and Human Services	DLBCL First-line ≥60 Stage: I/II=26% II/IV=74%	R-CHOP followed by maintenance rituximab or observation (n=267) Maintenance rituximab =174 Observation=178	Median age: 69 years (60-92) Male: 52% ECOG PS: 0=39%; 1=46%; 2=11%; 3=4%	Primary endpoint=FFS	Rituximab administered as induction or maintenance with CHOP chemotherapy significantly prolonged FFS in older DLBCL patients. After R-CHOP, no benefit was provided by maintenance rituximab
			CHOP followed by maintenance rituximab or observation (n=279)	Median age: 70 years (60-90) Male:48% ECOG PS: 0=42%; 1=44%; 2=10%; 3=4%		
Sonneveld 2006[25] (abstract only)	Phase III Multicentre The Netherlands, Sweden and Finland 20 months (3-46) Funding: not reported	Aggressive: DLBCL=80%; FL and MCL First-line >65 years Stage: NR	R-CHOP-14 or CHOP14 (n=243)	Median age: 72 years (65-85)	Primary endpoint: FFS	The CHOP14 regimen is tolerable and achievable in >60% of patients, and the addition of rituximab improves CR rate, OS and FFS

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Chamorey 2005[26]	Phase III Multicentre France 1994-1998 Funding: not reported	Aggressive First-line ≥65 years Stage: II=21% III/IV=79%	MEMID (n=72)	Median age: 72 years (65-84) Male: 61.1% WHO PS: 0=29.2%; 1=37.5%; 2=33.3%	Primary endpoint: compare OS, Secondary endpoints: EFS, RR and toxicity	The increased toxicity without survival benefit confirms the superiority of CHOP and CHOP-like regimens for elderly patients with aggressive NHL
			CEOP (n=77)	Median age: 72 years (65-86) Male: 48% WHO PS: 0=36.4%; 1=42.8%; 2=20.8%		
Bessell 2003[27]	Phase III Multicentre UK Follow-up 51 months (28-73) [for surviving patients] 1993-2000 Funding: Wyeth Laboratories	Aggressive: DLBCL=78%; Peripheral T-cell=3%; B-Cell lymphoma-uncassifiable=15% First-line ≥65 years Stage: I-II=62% III-IV=38%	CHOP (n=77)	Median age: 73 years (65-89) Male: 55% PS: 0=11%; 1=40%; 2=14%; 3=3%; 4=1%; Unknown=31%	Toxicity	This multicentre randomised trial provides further information on the dose intensity achievable with CHOP or MCOP regimens in elderly patients (median age 74 years) with aggressive NHL. These dose-reduced regimens can be given with nearly 100% dose intensity with 65% of patients completing all the treatment
			MCOP (n=78)	Median age: 74 years (65-91) Male: 35% PS:0=15%; 1=24%; 2=21%; 3=8%; 4=4%; Unknown=28%		
Doorduijn 2003[28]	Phase III Multicentre The Netherlands 33 months 1994-2000 Funding: Dutch National Health Council	Aggressive First-line ≥65 years Stage: II=25% III/IV=75%	CHOP (n=192)	Median age:72 years (65-90) Male: 57% WHO PS: 0-1=81%; 2-4=19%	RDI, CR, OS, EFS, PFS and DFS	In elderly patients, G-CSF improved the RDI of CHOP, but this did not lead to a higher CR rate or better OS. G-CSF did not prevent serious infections
			CHOP plus G-CSF (n=197)	Median age:72 years (65-90) Male: 54% WHO PS: 0-1=82%; 2-4=18%		

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Zinzani 2002[29]	Phase: NR Multicentre Italy Follow-up 32 months (3-62) 1996-2001 Funding: NR	Mixed disease types (DLBC/Anaplastic large B-cell/Peripheral T-cell/Other) First-line ≥60 years Stage: II=36% III/IV=64%	8-week VNCOP-B plus G-CSF (n=149)	Median age: 71 years (60-88) Male: 47.7% ECOG PS: 0-1=%; 2=19%; >2=8%	Efficacy and toxicity	Our data show that extending induction treatment with the VNCOP-B plus G-CSF regimen from 8 to 12 weeks does not raise the CR rate or provide a more durable remission
			12-week VNCOP-B plus G-CSF (n=148)	Median age: 70 years (60-89) Male: 54.7% ECOG PS: 0-1=74%; 2=16%; >2=10%		
Mainwaring 2001[30]	Phase III Multicentre UK Follow-up 20 months [26 for CR patients] 1993-1997 Funding: not reported	DLBCL First-line >60 years Stage: I/II=38% III/IV=62%	PAdriaCEBO (n=243)	Median age: 71 years (60-84) Male: 48% WHO PS: 0=20%; 1=46%; 2=24%; 3=9%; 4=1%	Efficacy, CSS and toxicity	The PMitCEBO 8-week combination chemotherapy regimen offers high response rates, durable remissions, and acceptable toxicity in elderly patients with high grade lymphoma
			PMitCEBO (n=230)	Median age: 71 years (60-85) Male: 51% WHO PS: 0=27%; 1=39%; 2=21%; 3=11%; 4=2%		
NHL – Indolent						
Foussard 2005[31]	Phase III Multicentre France 53 months (13-100) [surviving patients=70 (23-100)] 1995-1999 Funding: Schering SG	Indolent: FL=60% First-line ≥55 years Stage: II=4% III/IV=96%	FM (n=72)	Median age: 66 years (55-75) Male: 50.7% (FM=48.6%; mini-CHVP=52.7%) ECOG PS: >1=17% (FM=22%; mini-CHVP=11%)	Primary endpoint: response after 6 months (6 cycles) Secondary endpoints: response after 12 months (9 cycles), FFS, OS and safety outcome	FM was more effective than CHVP in achieving OR and CR, and favourably affected the outcome
			Mini-CHVP (n=72)			

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
NHL – Mixed or undefined						
Balducci 2007[32]	Phase IV Multicentre USA 2002-2004 Funding: Agmen Inc.	NHL type not specified First-line Stage: I/II=38% III/IV=62%	Pegfilgrastim in all cycles: CHOP=14% R-CHOP=84% EPOCH=2.7% (n=73) Pegfilgrastim at physicians discretion: CHOP=19% R-CHOP=81% (n=73)	Median age: 72 years (65-88) Male: 52% ECOG PS: 0=48%;1=45%; 2=6% Median age: 72 years (65-88) Male: 42% ECOG PS: 0=49%;1=44%; 2=6%	Primary endpoint: incidence of febrile neutropenia Secondary endpoints: incidence of grade 3 or 4 neutropenia and incidence of dose delays or reduction	Proactive pegfilgrastim use effectively produced a lower incidence of febrile neutropenia and related events in elderly patients with either solid tumours or NHL receiving an array of mild-to-moderately neutropenic chemotherapy regimens. Pegfilgrastim should be used proactively in elderly cancer patients to support the optimal delivery of standard chemotherapy
Mori 2005[33]	Phase III Multicentre Japan 96 months 1990-1991 Funding: NR	Various types First-line ≥65 years (>80=17.2%; >85=5.6%) Stage: I/II=31% III/IV=68%	THP-COP (n=153) CHOP (2nd/3rd dose) (n=140) THP-COPE (n=150)	Median age: 74 years (65-92) Male: 49% PS: 0-1=67%; 2-3=33% Median age: 74 years (65-92) Male: 57% PS: 0-1=70%; 2-3=30% Median age: 74 years (65-92) Male: 69% PS: 0-1=69%; 2-3=31%	NR	Pirarubicin may be more useful for T-cell lymphoma than doxorubicin. Because adverse cardiac events were reported only in CHOP, adverse cardiac events might be low in the THP group

DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MALT=mucosa-associated lymphoid tissue; NHL=non-Hodgkin's lymphoma; MCL=mantle cell lymphoma; CSS=cause-specific survival; DFS=disease-free survival; EFS=event-free survival; FFS=failure-free survival; PFS=progression-free survival; RFS=relapse-free survival;ORR=overall response rate; OS=overall survival; RR=response rate; TTF=time to treatment failure; TTP=time to disease progression; CR=complete response; RDI=relative dose intensity; QoL=quality of life; ECOG PS=Eastern Cooperative Oncology Group performance status; GELA=Groupe d'Etude des Lymphomes de l'Adulte; WHO=World Health Organisation; CEOP=cyclophosphamide, vincristine, epirubicin and prednisone; mini-CEOP=cyclophosphamide, epidoxorubicin, vinblastine and prednisone; R-CEOP=rituximab, epirubicin, cyclophosphamide, vincristine and prednisone; R-mini-CEOP=rituximab, epirubicin, cyclophosphamide, vinblastine and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; A-CHOP=amifostine plus CHOP; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; mini-CHVP=cyclophosphamide, doxorubicin, vindesine, and prednisone; ESHAP=etoposide, cisplatin, solumedrol, aracytine; EPOCH=eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone; FM=fludarabine, mitoxantrone; G-CSF=granulocyte colony-stimulating factor; GPD=gemcitabine, cisplatin, dexamethasone; IFN=interferon; MCOP=cyclophosphamide, mitozantrone, vincristine, prednisolone; MEMID=mitoxantrone, VP16, methylglyoxal, ifosfamide and dexamethasone; PAdriaCEBO=prednisolone, adriamycin, cyclophosphamide, etoposide, vincristine, and bleomycin; PMitCEBO=prednisolone, mitoxantrone, cyclophosphamide, etoposide, vincristine, and bleomycin; P-VEBEC=epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin and prednisone; R-FC=rituximab, fludarabine, and cyclophosphamide; THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone; THP-COPE=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone plus etoposide; VINCOP B=cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin and prednisone; NR=not reported

6.3 Efficacy evidence

Efficacy outcomes including overall survival (OS) and objective response rates (ORR) for all RCTs are presented in Table 5. A range of time-to-event outcomes were reported across (and within) the trials including: progression-free survival (PFS) in six trials,[16,17,20,21,28,33] event-free survival (EFS) in seven trials,[16,19-22,26,28] disease-free survival (DFS) in four trials,[16,17,21,28] time to disease progression (TTP) in one trial,[17] time to treatment failure (TTF) in one trial,[18] and failure-free survival (FFS) in five trials.[23-25,27,31] Reporting of survival outcomes also varied across all trials, and included 2-year OS,[26] 3-year OS,[16,20,24,33] 5-year OS,[16,19,21-23,26,28,29,33] 7-year survival,[31] 8-year OS,[17,33] 9-year OS,[24] 10-year OS,[21] 4-year survival,[18,30] in addition to median OS.[16,17,21,23,26,27]

Differences in the reporting of outcomes across trials make it difficult to synthesise and interpret the results in a clinically meaningful and relevant way.

6.3.1 Aggressive disease

Time-to-event outcomes

Failure-free survival was reported by four trials.[23-25,27] Haberman et al[24] reported that although no significant difference in survival was seen according to induction or maintenance therapy in older DLBCL patients, FFS was prolonged with maintenance rituximab (MR) after CHOP (p=0.0004) but not after R-CHOP (p=0.81), with 2-year FFS rates from second random assignment of 77%, 79%, 74%, and 45% for R-CHOP then observation, R-CHOP+MR, CHOP+MR, and CHOP then observation, respectively. In Sonneveld et al,[25] the CHOP-14 regimen was tolerable and achievable in >60 % of patients, and that the addition of rituximab improved the complete response (CR) rate, OS and FFS. The primary endpoint FFS was better in the R-CHOP-14 arm (38 failures: 9 non-responders, 29 relapses, 2-year FFS 55%) compared with the CHOP-14 arm (65 failures: 20 non-responders, 45 relapses, 2-year FFS 33%), with a hazard ratio (HR) of 0.60 (p=0.007). In the subgroup of DLBCL, FFS2yr was 62%, while log-rank OS (p=0.05) and FFS (p=0.004) were both superior with R-CHOP14.

Bessell et al[27] reported that the median FFS was 7 months longer for those randomised to CHOP (17 months, 95% CI 9–32 months) than for those allocated to MCOP (10 months, 95% CI 6–20 months), this did not translate into a significant difference between the two arms (χ^2=0.15, p=0.70). Patients with a low or intermediate/low risk, using the age-adjusted IPI, had a significantly longer survival than those with a intermediate/high or high risk (p<0.0001). The 3-year actuarial survival rate was 57% for those with a low or intermediate/low risk compared with 26% for those with an intermediate/high or high risk. Merli et al[23] reported that both Mini-CEOP and P-VEBEC determined a similar outcome for older patients with DLBLC, with a third of patients alive after more than 6 years of follow-up.

Event-free survival was reported by seven trials.[16,19-22,26,28] Aribi et al[20] reported that the gemcitabine-based therapy protocol was more effective and less toxic than ESHAP. The objective response rates and mean survival at 3 years were significantly higher among patients subjected to GPD treatment compared with those subjected to ESHAP treatment (63% vs. 55%, p=0.01 and 20.5% [95% CI 16.5-24.5] vs. 11.8% [95% CI 8.9-14.6], respectively). Additionally, 3-year PFS and EFS rates were 20.5% (95% CI 16.3-24) and 19.7% (95% CI 15.9-23.5), respectively, for the GPD regimen, and 10.9% (95% CI 8.2-13.7) and 11.1% (95% CI 8.5-13.7), respectively, for the ESHAP regimen. In Aviles et al,[22] rituximab did not improve the outcome in older patients with DLBCL and a poor prognosis. The EFS and OS were similar: 77% and 82%, respectively, in combined chemotherapy and 75% and 81% in the rituximab-chemotherapy regimen. In Chamorey et al,[26] the increased toxicity without survival benefit confirmed the superiority of CHOP and CHOP-like regimens for older patients with aggressive NHL. The median EFS was 8.5 months in the MEMID arm and 10.5 months in the CEOP arm (p=0.59). Doorduijn et al[28] reported EFS at 5 years as not different between patients treated with CHOP (18%) or CHOP plus G-CSF (17%; p=0.52). PFS was 24% and 25% in the CHOP and CHOP plus G-CSF arms, respectively (p=0.65).

Progression-free survival was reported by five trials.[16,17,20,21,28] In Coiffer et al,[21] for patients treated with R-CHOP the 10-year PFS was 36.5%, compared with 20.0% with CHOP alone, and the 10-year OS was 43.5% compared with 27.6%. In Doorduijn et al,[28] G-CSF improved the RDI of CHOP, but this did not lead to a higher CR rate or better OS. In Aribi et al,[20] the GPD regimen improved OR (response rate (RR)=2.02, 95% CI 1.59-2.56; p=0.000), EFS (RR=2.03, 95% CI 1.64-2.52; p<0.001) and PFS (RR=1.86, 95% CI 1.46-2.37; p<0.001). In Delarue et al,[16] the median PFS was not estimable. In Gomez et al,[17] A-CHOP was superior but without significance in 8-year PFS (72.9% vs 55.6%; p=0.50) or 8-year TTP (48.9% vs 36.3%; p=0.65).

Survival outcomes

Six of the trials[16,17,21,23,26,27] that focussed on aggressive disease reported median OS as a standard survival outcome. Gomez et al[17] reported the highest figure of 104.4/102 months for CHOP/A-CHOP (p=0.496), which was closely followed by Coiffier et al,[21] with a reported 100.8 months OS for R-CHOP versus 42 months for CHOP. The remaining results were lower, ranging from 15.4 months for the MEMID regimen to 20.3 months for the CEOP regimen.[26]

Rates for 5-year OS were well reported by the trials.[16,19,21-23,26,28,29] Aviles et al[22] reported the highest rates for 5-year OS with 82% for CEOP and 81% for R-CEOP; however, Chamorey et al[26] reported much lower results for CEOP (28.9%). CHOP-based regimens also attained some of the higher rates (>60%),[16,19] yet two trials had results of <60%[21] and <25%.[28]

Objective response rates

Objective response rates (ORR) were reported for all but three trials.[17,21,22] Eight of the trials[16,18,19,23-25,28,29] achieved an ORR of >70% in all treatment arms. The lowest ORR was reported by Aribi et al[20] for the ESHAP regimen (55%).

6.3.2 Indolent disease

Foussard et al[31] compared the efficacy and safety of FM with mini-CHVP in older patients with advanced, low-grade NHL. Median FFS for FM patients was 36 months (with a 4-year FFS of 42%), compared with 19 months for mini-CHVP patients (4-year FFS 10%); the results were statistically significant (p=0.0001).

In terms of survival, Foussard et al[31] reported 7-year survival of 53.5%, with no difference between the two treatment arms (p=0.94). For ORR, the result was statistically significant: 81% for FM versus 64% for mini-CHVP (p=0.0004).

6.3.3 Mixed or undefined disease

Mori et al[33] reported 3-, 5- and 8-year PFS rates for all patients, which were 31.3%, 21.9% and 15.2%, respectively. The 3-, 5- and 8-year survival rates for all patients were 40.4%, 29.4% and 18.7%, respectively. The 5- and 8-year survival rates were 27.4% and 17.4% for patients with aggressive lymphoma, respectively, compared with 48.2% and 36%, respectively, for those with low-grade lymphoma. Objective response rates were reported for the three treatment regimens (THP-COP, CHOP, THP-COPE) and were all similar (71.9%, 73.6%, 73.3%).

Table 5 Survival outcomes, randomised controlled trials

Study	Intervention	Time to event Months (95% CI)	Hazard ratio (95% CI)	Survival outcomes Months (95% CI)	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Aggressive							
Delarue 2013[16]	R-CHOP-14	3-year EFS=56 (50 to 62) Median EFS=68.6 months (41.7 to Not estimable) 3-year PFS=60% (54 to 65) 5-year PFS=53% (47 to 59) Median PFS=Not reached (47.3 to Not estimable) 3-year DFS=72% (66 to 78)	3-year EFS: HR=1.04 (0.82 to 1.31) p=0.7614 3-year PFS: HR=0.99 (0.78 to 1.26) p=0.8983 3-year DFS: HR=0.8 (0.58 to 1.1) p=0.1340	3-year OS=69% (64 to 72) 5-year OS=66% (60 to 71) Median OS=Not reached (75.4-Not estimable)	3 to year OS; HR=0.96 (0.73-1.26) p=0.7487	87%	p=0.6214
	R-CHOP-21	3-year EFS=60% (55 to 66) Median EFS=53.6 months (45.6 to Not estimable) 3-year PFS=62% (56 to 67) 5-year PFS=49% (43 to 56) Median PFS=59 months (48.5 to Not estimable) 3-year DFS=67% (61 to 73)		3-year OS=72% (67 to 77) 5-year OS=60% (53 to 66) Median OS=Not reached (76.1 to Not estimable)		86%	
Gomez 2013[17]	A-CHOP	8-year TTP=48.9% 8-year PFS=72.9% 8-year DFS=72.9%	TTP p=0.65 PFS p=0.50	8-year OS=44.3% Median OS=8.5 years (p=0.496)	Reported as not significant	NR	NR
	CHOP	8-year TTP=36.3% 8-year PFS=55.6% 8-year DFS=55.6%		8-year OS=54.4% Median OS=8.7 years			
Kluin-Nelemans 2012[18]	R-CHOP vs R-FC followed by maintenance rituximab or IFN	TTF=28 months (duration of remission=36 months)	NR	4-year survival=62%	HR=1.50 (1.13 to 1.99) p=0.005	86%	
	R-FC	TTF=26 months (Remission duration=37 months)	NR	4-year survival=47%		78%	
	Rituximab maintenance	NR	NR	4-year survival=79%	p=0.13	NR	NR
	IFN maintenance	NR	NR	4-year survival=67%			
	R-CHOP with R maintenance	NR	NR	87%	p=0.005		
	R-CHOP with IFN	NR	NR	63%			

Study	Intervention	Time to event Months (95% CI)	Hazard ratio (95% CI)	Survival outcomes Months (95% CI)	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Merli 2012[19]	All patients	2-year EFS=55% (49 to 62) Estimated 5-year EFS=47% (40 to 54)	NR	5-year OS=62% (55 to 69)	NR	NR	NR
	R-CHOP	2-year EFS=57% Estimated 5-year EFS=48% (37 to 58)	5-year EFS: p=0.538 HR=1.12 (0.78 to 1.6) Age >72 had a better outcome than those <72; HR=1.38 (0.95 to 2), p=0.088	5-year OS=62% (51 to 71)	p=0.702 Age >72 had a better outcome than those <72; HR=1.58 (1.02 to 2.48) p=0.046	87%	p=0.284
	R-mini-CEOP	2-year EFS=54% Estimated 5-year EFS=46% (36 to 55)		5-year OS=63 (52 to 72)		81%	
Aribi 2010[20]	ESHAP	3-year PFS=10.9% (8.2 to 13.7) 3-year EFS=11.1% (8.5 to 13.7)	EFS ESHAP vs GPD: RR=2.03 (1.64 to 2.52) p=0.0001 PFS ESHAP vs GPD: RR=1.86 (1.46 to 2.37) p=0.0003	3-year OS=11.8% (8.9 to 14.6)	OS ESHAP vs GPD; RR=2.02 (1.59 to 2.56) p=0.000 3-year OS p=0.001	55%	p=0.01
	GPD	3-year PFS=20.5% (16.3 to 24) 3-year EFS=19.7% (15.9 to 23.5)		3-year OS=20.5% (16.5 to 24.5)		63%	
Coiffier 2010[21]	R-CHOP	10-year PFS=36.5% (29.7 to 43.3) Median PFS=57.6 months (32.4 to 91.2) 10-year DFS=64.3% (55.4 to 71.9) 5-year DFS=66% (56.2 to 74) Median DFS=Not reached At 5-years, median EFS=45.6 months (28.4 to not reached) 5-year EFS=47% (39.9 to 54.1)	Median PFS: p<0.0001 Median DFS: p<0.0001	10-year OS=43.5% (36.4 to 5.4) 5-year OS=58% (50.8 to 64.5) Median OS=100.8 months (64.8 to not reached) After progression: Median OS=0.7 months 5-year OS=25% 10-year OS=8.6%	10-year OS p<0.0001	NR	NR
	CHOP	10-year PFS=20.1% (14.6 to 26.2) Median PFS=14.4 months (10.8 to 21.6) 10-year DFS=42.6% (33.6 to 51.4) 5-year DFS=45% (36.6 to 55.3) Median DFS=40.8 (19.2 to not reached)		10-year OS=27.6% (21.4 to 34.3) 5-year OS=45% (39.1 to 53.3) Median OS=42 months (26.4-66) After progression: Median OS=0.6 months 5 to year OS=14.6%			

Study	Intervention	Time to event Months (95% CI)	Hazard ratio (95% CI)	Survival outcomes Months (95% CI)	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
		At 5-years, median EFS=13.2 months (9.6 to 18) 5-year EFS=29% (23.1 to 35.8)		10-year OS=10.5%			
Aviles 2007[22]	CEOP	5-year EFS=77%	p=0.66	5-year OS=82%	p=0.73	NR	NR
	R-CEOP	5-year EFS=75%		5-year OS=81%			
Merli 2007[23]	All patients	5-year FFS=21%	NR	5-year OS=32%	Age as variable, p<0.001	NR	NR
	Mini-CEOP	NR		Median OS=18 months	NR	78%	p=0.021
	P-VEBEC	NR		Median OS=20 months		90%	
Habermann 2006[24]	R-CHOP	3-year FFS=53% 9-year FFS=35%	3-year; HR=0.78 (0/61 to 0.99) p=0.04 9-year; p=0.008	3-year OS=67% 9-year OS=44%	3-year: HR=0.83 (0.63 to 1.09) p=0.18 9-year: p=0.11	77%	NR
	CHOP	3-year FFS=46% 9-year FFS=25%		3-year OS=58% 9-year OS=37%		76%	
	Maintenance rituximab	2-year FFS=76%	HR=0.63 (0.44 to 0.9) p=0.009	NR	HR=0.96 (0.63 to 1.47) p=0.85	NR	
	Observation	2-year FFS=61%					
	R-CHOP then observation	2-year FFS=77% TTP=102 months	FFS: HR=0.93 (0.53 to 1.66) p=0.81		NR		
	R-CHOP + maintenance rituximab	2-year FFS=79% TTP=90 months					
	CHOP + maintenance rituximab	2-year FFS=74% TTP=114 months	FFS: HR=0.45 (0.29 to 0.71) p=0.0004 TTP: p=0.003				
	CHOP then observation	2-year FFS=45% TTP=24 months					
	R-CHOP ≥70	3-year FFS=49% (40 to 58)	RR=(1.7 (1.2 to 2.4) p=0.002	3-year OS=58% (49 to 66)	HR=58 (49 to 66) p=0.002		
	R-CHOP 60-69	3-year FFS=64% (56 to 72)		3-year OS=74% (72 to 82)			
	R-CHOP IPI HI	3-year FFS=56%	p<0.01	3-year OS=68%	p<0.01		
	R-CHOP IPI H	3-year FFS=33%		3-year OS=43%			
	R-CHOP aaIPI HI	3-year FFS=47%	p<0.001	3-year OS=59%	p<0 .01		
	R-CHOP aaIPI H	3-year FFS=31%		3-year OS=35%			
Sonneveld 2006[25] (abstract only)	R-CHOP-14	2-year FFS=55%	HR=0.6 p=0.007	NR	HR=0.69, 95% CI 0.46 to 1.05, p=0.09	92%	
	CHOP-14	2-year FFS=33%				83%	
Chamorey 2005[26]	MEMID	EFS 8.5 (6.9 to 17.9) 2-year EFS=16% (9 to 28.7)	Median EFS: p=0.47 2-year EFS: p=0.19	15.4 (8.2 to 37.8) 2-year OS=29.8% (20.1 to 44.1) 5-year OS=24.8% (14.6 to 42.2)	Median OS: p=0.59 2-year OS: p=0.70 5-year OS:	55.5%	p=0.24

Study	Intervention	Time to event Months (95% CI)	Hazard ratio (95% CI)	Survival outcomes Months (95% CI)	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
				For survivors, range=0 to 78.3 months	p=0.66		
	CEOP	10.5 (8.74 to 13.6) 2-year EFS=4.7% (1.6 to 14)		20.3 (13.0 to 38.2) 2-year OS=33.2% (23.4 to 46.6) 5-year OS=28.9% (18.7 to 44.5) For survivors, range=0 to 74.9 months		64.9%	
Bessell 2003[27]	CHOP vs MCOP All patients			Median survival=19 months (10 to 36) 2-year actuarial survival=47% 3-year actuarial survival=42%			
	CHOP	FFS=17 months (9 to 32)	p=0.70	Median survival=20 (10 to 42)	CHOP vs MCOP, p=0.79	78%	
	MCOP	FFS=10 months (6 to 20)		Median survival=16 months (8 to 47)		67%	
Doorduijn 2003[28]	CHOP	5-year EFS=18% 5-year PFS=24% 5-year DFS=43%	EFS: p=0.52 PFS: p=0.65 DFS: p=0.31	5-year OS=22%	p=0.76	83%	p=0.7
	CHOP plus G-CSF	5-year EFS=17% 5-year PFS=25% 5-year DFS=40%		5-year OS=24%		85%	
Zinzani 2002[29]	VNCOP-B +G-CSF (8-week)	NR	NR	5-year OS=52%	p=0.01	87%	NR
	VNCOP-B +G-CSF (12-week)			5-year OS=37%		84%	
Mainwaring 2001[30]	PAdriaCEBO	NR	NR	4-year OS=28% 4-year CSS=35%	PMitCEBO OS was significantly better p=0.0067 4-year OS: p<0.001 4-year CSS: p<0.001	69%	p=0.05
	PMitCEBO			4-year OS=50% 4-year CSS=59%		78%	

Study	Intervention	Time to event Months (95% CI)	Hazard ratio (95% CI)	Survival outcomes Months (95% CI)	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Indolent							
Foussard 2005[31]	FM	FFS=36 months 4-year FFS=42%	p=0.0001	7-year survival=53.5%	No difference between treatment arms (p=0.94)	81%	p=0.0004
	Mini-CHVP	FFS=19 months 4-year FFS=10%				64%	
Mixed/Unclear							
Mori 2005[33]	All patients	3-year PFS=31.3% 5-year PFS=21.9% 8-year PFS=15.2%	NR	3-year OS=40.4% 5-year OS=29.4% 8-year OS=18.7%	NR	NR	NR
	Aggressive lymphoma	NR		5-year survival=27.4% 8-year survival=17.4% 48.2% and 36% for low grade		NR	
	THP-COP	NR		5-year survival=30.3%		71.9%	
	CHOP	NR		5-year survival=25%		73.6%	
	THP-COPE	NR		5-year survival=26.4%		73.3%	

CSS=cause-specific outcome; DFS=disease-free survival; EFS=event-free survival; FFS=failure-free survival; PFS=progression-free survival; ORR=overall response rate; OS=overall survival; TTF=time to treatment failure; TTP=time to disease progression; CI=confidence inetravl; HR=hazard ratio; RR=response rate; IPI=International Prognostic Index; aaIPI=age-adjusted IPI; HI=high-to-intermediate risk; H=high risk; CEOP=cyclophosphamide, vincristine, epirubicin and prednisone; mini-CEOP=cyclophosphamide, epidoxorubicin, vinblastine and prednisone; R-CEOP=rituximab, epirubicin, cyclophosphamide, vincristine and prednisone; R-mini-CEOP=rituximab, epirubicin, cyclophosphamide, vinblastine and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; A-CHOP=amifostine plus CHOP; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; mini-CHVP=cyclophosphamide, doxorubicin, vindesine, and prednisone; ESHAP=etoposide, cisplatin, solumedrol, aracytine; EPOCH=eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone; FM=fludarabine, mitoxantrone; G-CSF=granulocyte colony-stimulating factor; GPD=gemcitabine, cisplatin, dexamethasone; IFN=interferon; MCOP=cyclophosphamide, mitozantrone, vincristine, prednisolone; MEMID=mitoxantrone, VP16, methylglyoxal, ifosfamide and dexamethasone; PAdriaCEBO=prednisolone, adriamycin, cyclophosphamide, etoposide, vincristine, and bleomycin; PMitCEBO=prednisolone, mitoxantrone, cyclophosphamide, etoposide, vincristine, and bleomycin; P-VEBEC=epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin and prednisone; R-FC=rituximab, fludarabine, and cyclophosphamide; THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone; THP-COPE=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone plus etoposide; VINCOP B=cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin and prednisone; NR=not reported

6.4 Tolerability evidence

Sixteen trials[16-24,26-28,30-33] reported outcomes of interest; details are presented in Table 6.

6.4.1 Aggressive disease

Treatment completion was reported either as a proportion of the planned treatment received, or as a proportion of patients who completed the planned treatment. Two trials[16,26] reported the rate of treatment completion. Delarue et al[16] reported that for the treatment regimens of R-CHOP-14 and R-CHOP-21, 72% and 79% of patients received all 8 cycles, respectively. Chamorey et al[26] reported the median number of cycles completed per patient, alongside the proportions of patients who completed >3 and all 6 cycles for the MEMID and CEOP arms, respectively (6, 73.6%, 56.9% vs 6, 79.2%, 71.4%). Three trials[19,27,28] reported information relating to dose intensity. In Merli et al,[19] the median dose intensity was 0.92 (range 0.68-1) for R-CHOP and 0.96 (range 0.77-1.1)for R-mini-CEOP. Doorduijn et al[28] reported a median dose intensity of 93.4 (range 47.7-109) for CHOP and 95.1 (range 39.4-110) for CHOP G-CSF. Bessell et al[27] reported a median dose intensity of 97% across both trial arms.

Treatment discontinuations and withdrawals were not well reported across the trials. In Merli et al[19] 12 patients in the mini-CEOP arm, and 9 patients in the R-CHOP arm discontinued treatment. In Bessell et al,[27] 35% of all patients discontinued treatment (30% in the CHOP arm and 40% in the MCOP arm). Doorduijn et al[28] reported that 32% of patients discontinued treatment in the CHOP arm, compared with 31% in the CHOP G-CSF arm, with toxicity being the main factor responsible for discontinuation. Chamorey et al[26] reported a higher proportion of discontinuations for MEMID (25%) compared with CEOP (9.1%), and Merli et al[23] reported discontinuations of 9% for all patients.

Across the trials, grade 3-4 AEs were well reported. Neutropenia, anaemia, thrombocytopenia and leukopenia were commonly reported haematological AEs. Where reported, neutropenia ranged from 13%[17] to 84.7%[26] across trials. Rates of anaemia were generally low, but ranged from 10%[20] to 52.8%.[26] Rates of thrombocytopenia ranged from 9%[16] for R-CHOP to 63%[20] for ESHAP (vs 31% for GDP, $p<0.01$). For leukopenia, the lowest reported figure was 7%[20] and the highest figure reported was 73%.[18] Infection was also commonly reported: Aribi et al[20] reported the highest infection rates (20% and 29%), and Delarue et al[16] reported the lowest infection rate (10%).

Non-haematological AEs were reported less frequently. The highest rate of alopecia was reported by Coiffier et al[21] (39%, 45%), and the lowest rates were reported by Bessell et al[27] (12% and 5%). Habermann et al[24] reported non-haematological toxicity of 17% and 18%. Aribi et al[20] reported rates of vomiting at 29.3% and 31.4%, which was higher than the 10% and 15% reported for nausea/vomiting by Bessell et al.[27]

6.4.2 Indolent disease

Foussard et al[31] compared FM with mini-CHVP. In the FM arm, 569 cycles were administered, and 72% of patients received all of the planned cycles. In the mini-CHVP arm, 560 cycles were administered and 66% of patients received the planned 9 cycles. The primary reason for discontinuation was progression/early failure (29 patients). In terms of grade 3-4 AEs, neutropenia was experienced by >50% of patients in both arms. Alopecia was much higher in the mini-CHVP arm (41%) compared with the FM arm (9%).

6.4.3 Mixed or undefined disease

Balducci et al[32] reported that 52% of patients across treatment arms completed the planned chemotherapy. Across treatment arms the reasons for discontinuation were AEs (16%), investigators decisions (7%) and death (7%). Dose reductions were necessary in 16% and 8% of patients in the respective trial arms, and dose delays were experienced by 29% and 23% of patients. Figures for febrile neutropenia were high in both arms (>75%). Mori et al[33] reported that >70% of patients in each arm received >3 cycles. Grades 3 and 4 neutropenia were reported; the lowest rates were in the CHOP arm.

Table 6 Tolerability, randomised controlled trials

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Aggressive				
Delarue 2013[16]	R-CHOP-14 72% received all 8 cycles	NR	Adaptation of dosage regimen=12% Permanently stopped at least 1 drug due to toxicity=21%	Neutropenia: Grade 3=15%, grade 4=59% Grade 3: Anaemia=18% Thrombocytopenia=9% Febrile neutropenia=21% Infection=10% Toxic death=13%
	R-CHOP-21 79% received all 8 cycles	NR	Adaptation of dosage regimen=13% Permanently stopped at least 1 drug due to toxicity=19%	Neutropenia: Grade 3=14%, grade 4=51% Grade 3: Anaemia=14% Thrombocytopenia=10% Febrile neutropenia=18% Infection=12% Toxic death=13%
Gomez 2013[17]	NR	NR	NR	A-CHOP Neutropenia=13% Febrile neutropenia=3%
	NR	NR	NR	CHOP Neutropenia=27% (p=0.007) Febrile neutropenia 10% (p=0.056)
Kluin-Nelemans 2012[18]	NR	NR	NR	R-CHOP Grade 3-4 toxicity: Infection=14% Febrile neutropenia=17% Anaemia=12% Leukocytopenia=59% Lymphocytopenia=69% Neutropenia=60% Thrombocytopenia=18%
	NR	NR		R-FC Grade 3-4: Infection=17% Febrile neutropenia=11% Anaemia=20%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				Leukocytopenia=73% Lymphocytopenia=78% Neutropenia=69% Thrombocytopenia=41%
Merli 2012[19]	NR	NR	NR	All patients 13 out of the 21 patients who discontinued died after the event Treatment related deaths=4 patients
	R-CHOP Median dose intensity=0.92 (range 0.68-1)	Discontinuations=9 patients	NR	Grade 3-4 neutropenia=23% Treatment-related mortality=9.1%
	R-mini-CEOP Median dose intensity=0.96 (range 0.77-1.1)	Discontinuations=12 patients	NR	Grade 3-4 neutropenia=23% Treatment-related mortality=6.1%
Aribi 2010[20]	NR	NR	NR	ESHAP: Grade 3-4 toxicities: Leukopenia=7% Thrombocytopenia=63% Anaemia=11.5% Infection=20% Vomiting=31.4%
	NR	NR	NR	GPD: Grade 3-4 toxicities: Leukopenia=18.2% (p<0.01) Thrombocytopenia=31% (p<0.01) Anaemia=10% Infection=29% Vomiting=29.3%
Coiffier 2010[21]	NR	NR	NR	R-CHOP Grade 3-4 toxicities: Infection=12% Lung toxicity=8% Alopecia=39% Other=20% Toxic death=13%
	NR	NR	NR	CHOP Grade 3-4 toxicities: Infection=20% Lung toxicity=11%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				Alopecia=45% Other=25% Toxic death=11%
Aviles 2007[22]	NR	NR	CEOP 11 patients unable to receive escalated epirubicin after the 3rd cycle	NR
	NR	NR	R-CEOP 17 patients unable to receive escalated epirubicin after the 3rd cycle	NR
Merli 2007[23]	NR	All: Discontinuations=21 patients (9%), due to toxicity	NR	NR
	NR	Mini-CEOP Discontinuations=10 patients (8%), due to toxicity	NR	Grade 3-4 neutropenia=17% Treatment-related deaths=10/125
	NR	P-VEBEC Discontinuations=11 patients (10%), due to toxicity	NR	Grade 3-4 neutropenia=39%, p=0.049 Treatment-related deaths=7/107
Habermann 2006[24]	NR	NR	NR	R-CHOP Grade 3-4: Neutropenia=78% Anaemia=17% Thrombocytopenia=14% Infection=17% Lethal toxicity=13 patients
	NR	NR	NR	CHOP: Grade 3-4: Neutropenia=78% Anaemia=16% Thrombocytopenia=10% Infection=16% Lethal toxicity=12 patients
	NR	NR	NR	Maintenance rituximab Grade 3-4: Granulocytopenia=12% Non-haematological toxicity=18%
	NR	NR	NR	Observation

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				Grade 3-4: Granulocytopenia=4% (p=0.008) Non-haematological toxicity=17% (p=0.69)
Chamorey 2005[26]	MEMID Median cycles per patient=6 (range 1-6) 73.6% >3cycles 56.9% completed all 6 cycles	Discontinuations=25%	NR	Grade 3-4: Neutropenia=84.7% Anaemia=52.8% Thrombocytopenia=33.4% 4 toxic deaths
	CEOP Median cycles per patient=6 (range 0-6) 79.2% >3 cycles 71.4% completed all 6 cycles	Discontinuations=9.1%	NR	Grade 3-4: Neutropenia=28.6% ($p < 10^{-5}$) Anaemia=11.7% ($p < 10^{-5}$) Thrombocytopenia=10.4 (p=0.0006) 2 toxic deaths
Bessell 2003[27]	All patients Median dose intensity=97%	Discontinuations=35%	NR	Grade 3-4 neutropenia=30%
	NR	CHOP Discontinuations=30%	A median delay of a week was experienced for administering 55 (14%) cycles (range 3–35 days) Dose reductions=41 (10%) cycles	Grade 3-4 toxicity: Neutropenia=42% Leukopenia=35% Nausea/vomiting=10% Alopecia=12%
	NR	MCOP Discontinuations=40%	A median delay of a week was experienced for administering 53 (14%) cycles (range 1–42 days) Dose reductions=42 (11%) cycles	Grade 3-4 toxicity: Neutropenia=55% Leukopenia=59% Nausea/vomiting=15% Alopecia=5%
Doorduijn 2003[28]	CHOP Median dose intensity=93.4 (range 47.7-109)	Discontinuations=32% Due to: Toxicity=16% (13%) Progression/relapse=6% (9%) Death=5% Refusal=2% No response=2% Other=2%	NR	NR
	CHOP G-CSF Median dose intensity=95.1 (range 39.4-110)	Discontinuations=31% Due to: Toxicity=11% Progression/relapse=11% Death=4%	NR	NR

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		Refusal=3% No response=1% Other=3%		
Mainwaring 2001[30]	NR	NR	NR	PAdriaCEBO Grade 3-4 toxicity: Leukopenia=51% Alopecia=31% Treatment-related death=22 patients
	NR	NR	NR	PMitCEBO Grade 3-4 toxicity: Leukopenia= 65.7%, p=0.02 Alopecia=25%, p=0.12 Treatment-related deaths=11 patients (p=0.10)
Indolent				
Foussard 2005[31]	FM Cycles administered=569 Received the planned 9 cycles=72%	Discontinuations due to: Death=2 patients (pneumonia and pulmonary embolism) Transformation to aggressive=1 patient Progression/early failure=29 patients Haemolysis=1 patient Sepsis=3 patients Cytopenia – 4 patients Concomitant cancer=1 patient	NR	Grade 3-4 toxicities: Alopecia=9% Infections=14% Herpes zoster=12% Thrombocytopenia=12% Neutropenia=64% Fever=10%
	Mini-CHVP Cycles administered=560 Received the planned 9 cycles=66%		NR	Grade 3-4 toxicities: Alopecia=41% Infections=5% Herpes zoster=0% Thrombocytopenia=3% Neutropenia=54% Fever=2%
Mixed/Unclear				
Balducci 2007[32]	Pegfilgrastim in all cycles: CHOP/R-CHOP/EPOCH 52% completed planned chemotherapy	Discontinuations=5.5% (4 patients)	Dose delays=29% (16-41) Dose reduction=16% (9-27)	Grade 3-4 febrile neutropenia=82% (72-90) Grade 4 febrile neutropenia=75% (64-85)

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
	Pegfilgrastim at physician's discretion: CHOP/R-CHOP 52% completed planned chemotherapy	Discontinuations=19% (14 patients), Discontinuations both arms: AEs=16% Investigators decisions=7% Death=7%	Dose delays=23% (14-35) Dose reduction=8% (3-17)	Grade 3-4 febrile neutropenia=90% (81-96) Grade 4 febrile neutropenia=86% (76-93)
Mori 2005[33]	THP-COP 76.5% received >3 cycles	NR	NR	Neutropenia Grade 3=28.8% Grade 4=15.4%
	CHOP 70% received >3 cycles	NR	NR	Neutropenia Grade 3=21.4% Grade 4=7.1%
	THP-COPE 72.3% received >3 cycles	NR	NR	Neutropenia Grade 3=35.1% Grade 4=14.6%

AE=adverse event; CEOP=cyclophosphamide, vincristine, epirubicin and prednisone; mini-CEOP=cyclophosphamide, epidoxorubicin, vinblastine and prednisone; R-CEOP=rituximab, epirubicin, cyclophosphamide, vincristine and prednisone; R-mini-CEOP=rituximab, epirubicin, cyclophosphamide, vinblastine and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; A-CHOP=amifostine plus CHOP; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; mini-CHVP=cyclophosphamide, doxorubicin, vindesine, and prednisone; ESHAP=etoposide, cisplatin, solumedrol, aracytine; EPOCH=eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone; FM=fludarabine, mitoxantrone; G-CSF=granulocyte colony-stimulating factor; GPD=gemcitabine, cisplatin, dexamethasone; MCOP=cyclophosphamide, mitozantrone, vincristine, prednisolone; MEMID=mitoxantrone, VP16, methylglyoxal, ifosfamide and dexamethasone; PAdriaCEBO=prednisolone, adriamycin, cyclophosphamide, etoposide, vincristine, and bleomycin; PMitCEBO=prednisolone, mitoxantrone, cyclophosphamide, etoposide, vincristine, and bleomycin; P-VEBEC=epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin and prednisone; THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone; THP-COPE=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone plus etoposide; NR=not reported

6.5 Geriatric assessment and quality of life

Summary outcomes relating to CGA and quality of life (QoL) reported in the trials are presented in Table 7. Full details are presented in Appendices 4 and 5.

Comprehensive geriatric assessment

One trial reported CGA outcomes. Merli et al[19] used the Instrumental Activities of Daily Living (IADL) as a baseline measure to assess patient fitness at enrolment.

Quality of life

Two of the included trials[23,28] measured QoL as an outcome measure. Both trials used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). Both trials found that patient QoL was improved after treatment.

Table 7 Comprehensive geriatric assessment and quality of life, randomised controlled trials

Study	Geriatric assessment		Quality of life	
	Tool(s) used	How tool was used	Tool(s) used	Author conclusions
Merli 2007[23]	NR	NR	EORTC QLQ-C30 questionnaire	The EORTC QLQ-C30 is feasible even in a population of elderly patients, in whom it had never been tested before. The improvement of QoL at the end of the treatment demonstrated that the symptoms of the disease have a greater negative influence on the patient's life than do the side-effects of the therapy
Merli 2012[19]	IADL	Baseline measure to assess patient fitness at enrolment	NR	NR
Doorduijn 2003[28]	NR	NR	EORTC QLQ-C30 questionnaire	The QoL significantly improved during CHOP in patients with B symptoms (fever, weight loss, night sweats), and remained equal in all other patients. This implies that a poor QoL before start of CHOP is no reason to adjust treatment. G-CSF had no effect on the QoL. After completion of treatment, most chemotherapy-related symptoms disappeared, and the patients' QoL improved rapidly

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; IADL=Instrumental Activities of Daily Living; QoL=quality of life; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; G-CSF=granulocyte colony-stimulating factor; NR=not reported

6.6 Summary and discussion

A total of 18 RCTs[16-33] enrolling only older people were included in the review. The large volume of evidence available reflects the prevalence of NHL in the older population; unfortunately, synthesis of the evidence was difficult due to the poor methodological quality and relatively small size of the included trials. However, many of the included trials have helped to shape UK clinical practice, and it must be noted that conducting good-quality trials to treat a complex, heterogeneous disease can prove challenging. The majority of trials were phase III, with several trials conducted in Europe and two trials based in the UK.

The trials focussed predominantly on patients with aggressive disease, and although several subtypes of NHL were included, the most common subtype was DLBCL. Across trials, a large number of different treatments were administered; the most frequent were R-CHOP and CHOP. The definition of older (minimum age for entry into a trial) varied across the trials, and ranged from 60 to 92. Where reported, the majority of patients recruited to the trials had a PS of 0 or 1.

Efficacy outcomes were well reported, with a variety of efficacy outcome measures reported across trials (PFS, TTP, EFS, DFS, TTF, FFS, OS, ORR). Due to the heterogeneous nature of the patient populations and the variance in treatment regimens, it was impossible to draw any firm conclusions; however, the general trends showed that older patients derived benefit from treatment, in terms of response and survival.

Tolerability outcomes, such as RDI, discontinuations and withdrawals, and dose modifications or reductions were not well reported, although grade 3-4 AEs were well reported across the trials. Commonly reported haematological AEs were neutropenia, anaemia, thrombocytopenia and leukopenia. The most common non-haematological AEs were alopecia and nausea/vomiting.

Based on authors' conclusions, the results of the trials show that, in general, chemotherapy is effective and tolerable, with acceptable toxicity in fit older patients with NHL. Most of the chemotherapy regimens were found to be effective, however, many authors recommend further trials in specific populations of older patients to determine the most appropriate treatments for subtypes.

7 POOLED ANALYSES OF RANDOMISED CONTROLLED TRIALS

One study[48] that pooled data from two trials was included in the review. Study characteristics are presented in Table 8.

7.1 Study characteristics

The pooled analysis reported by Fridrik et al[48] was derived from two consecutive trials conducted in Austria. The first trial was conducted from 1988 to 1991, and the second trial was conducted between 1991 and 1995. The study investigated the use of first-line CEOP/IMVP-Dexa (cyclophosphamide, epirubicin, vincristine, prednisolone/ifosfamide, uromitexan, VP-16, dexamethasone, methotrexate and Ca folinate) with and without filgrastim. The first study was a phase II trial designed to assess feasibility, toxicity and efficacy, and the second study was an open-label phase III trial of CEOP/IMVP-Dexa alternating chemotherapy and filgrastim versus CEOP/IMVP-Dexa alternating chemotherapy.

The study focussed on patients with aggressive disease, and included patients with various disease stages (I=15.5%; II=35.9%; III=16.9%; IV=31.7%). The majority (82%) of patients had DLBCL. Forty-eight patients (33.8%) were aged >60 years, and the median age of the patients was 52 years (range: 19-72 years). The majority of patients had an IPI score related to low risk.

The study concludes that while the regimen could be superior over standard CHOP regimens, further studies need to be conducted – and it must be noted that the conclusions are generalised to the whole study population rather than for older patients specifically.

Table 8 Study characteristics, pooled analyses

Study	Details	Population	Intervention	Baseline	Purpose	Conclusions
Fridrik 2005[48]	Multicentre Austria Follow-up 96 months 1988-1991/1991-1995	DLBCL: 82% First-line >60=33.8% Stage : I=15.5% II=35.9% III=16.9% IV=31.7%	CEOP/IMVP-Dexa (n=142)	Median age: 52 years (19-72) IPI: L=50%; LI=24%; HI=18%; H=8%	To evaluate the long-term outcome of dose density chemotherapy in the treatment of aggressive lymphoma	The excellent long-term results of the CEOP/IMVP-Dexa regimen for patients aged ≤60 years suggest that this regimen might be superior to the standard CHOP regimen and needs to be tested in comparison with high-dose regimens and novel approaches including antibody treatment

DLBLC=diffuse large B-cell lymphoma; CEOP/IMVP-Dexa=cyclophosphamide, epirubicin, vincristine, prednisolone/ifosfamide, uromitexan, VP-16, dexamethasone, methotrexate and Ca folinate; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; IPI=International Prognostic Index; L=low risk; LI=low-to-intermediate risk; HI=high-to-intermediate risk; H=high risk

7.2 Efficacy evidence

Outcomes relating to OS, TTF and time to relapse (TTR) were reported in the included pooled analysis.[48] Results are presented in Table 9.

There was no TTR reported for patients aged >60; however, the overall HR for TTF for all patients at 8 years was 0.536 (95% CI 0.457-0.63). The HR for TTR at 8 years for patients with a CR was 0.619 (95% CI 0.53-0.72).

The pooled analysis reported statistically significant OS results between older and younger patients. The OS for all patients at 8 years was 0.583 (95% CI 0.503-0.665). The 8 year OS was 0.713 (95% CI 0.662-0.816) for patients ≤60, and 0.304 (95% CI 0.192-0.543; p<0.001) for patients aged >60 years. The ORR was only reported for the overall population (92.3%).

Table 9 Efficacy outcomes, pooled analyses

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Fridrik 2005[48]	CEOP/IMVP-Dexa All patients	NR	8-year TTF=0.536 (0.457-0.63) 8-year TTR (patients with CR)=0.619 (0.53-72)	NR	8-year OS=0.583 (0.503-0.665)	92.3%	NR
	≤60	NR	NR	NR	8-year OS=0.713 (0.662-0.816)	NR	
	>60	NR	NR	NR	8-year OS=0.304 (0.192-0.543) p<0.001	NR	

CEOP/IMVP-Dexa=cyclophosphamide, epirubicin, vincristine, prednisolone/ifosfamide, uromitexan, VP-16, dexamethasone, methotrexate and Ca folinate; PFS=progression-free survival; TTP=time to progression; TTF=time to treatment failure; TTR=time to relapse; CR=complete response; OS=overall survival; ORR=overall response rate; CI=confidence interval; NR=not reported

7.3 Tolerability evidence

The study[48] did not report any outcomes relating to tolerability.

7.4 Geriatric assessment and quality of life

The study[48] did not report outcomes relating to CGA or QoL.

7.5 Summary and discussion

Fridrik et al[48] pooled data from two consecutive trials and focused on patients with aggressive disease (predominantly DLBCL). The study evaluated the treatment regimen of CEOP/IMVP-Dexa with and without filgrastim. The median age of the patients was 52 years (range: 19-72 years).

Outcomes were poorly reported. However, a statistically significant OS result was reported between older and younger patients: younger patients had a significantly higher OS at 8 years than older patients ($p<0.001$). There were no QoL or CGA results reported.

From these long-term results of the CEOP/IMVP-Dexa regimen, the authors concluded that, for patients aged ≤60 years, this regimen might be superior to the standard CHOP regimen, but it needs to be tested in comparison with high-dose regimens and novel approaches, including antibody treatment.

8 COMPARATIVE COHORTS

Four studies[49-52] comparing two or more non-randomised treatment arms that included older patients were included in the review. Details of the study characteristics are presented in Table 10.

8.1 Study characteristics

Two studies[49,50] focussed on patients with aggressive disease, one study[51] focussed on patients with indolent disease, and one study[52] included mixed or undefined populations.

8.1.1 Aggressive disease

Two studies[49,50] focussed on patients with DLBLC. Lee et al[50] did not report detailed study characteristics; the study was conducted in Korea between 1994 and 2000. Tholstrup et al[49] was a single centre study conducted in Denmark between 2002 and 2003, and was funded by the Danish Cancer Society and the University of Copenhagen. Tholstrup et al[49] included first-line patients; the line of treatment was unclear in Lee et al.[50]

Tholstrup et al[49] treated all patients with CHOP-14, and two cohorts were compared – patients at high risk (including older patients with a higher PS) versus those patients with standard risk (older patients, and younger patients with a high PS). Lee et al[50] compared CHOP with COPBLAM-V (cyclophosphamide, vincristine, bleomycin, doxorubicin, procarbazine and prednisone) and recorded data for patients aged <60 and >60 years. The study numbers were relatively small: Tholstrup et al[49] reported outcomes for 65 patients, some of whom were not considered older but had a low PS; Lee et al[50] included 195 patients, but only 36% were aged >60.

The study populations varied greatly both between arms, and across studies. The median age of the very high risk cohort in Tholstrup et al[49] was 76 years. In Lee et al,[50] the median age for those aged >60 years was 69. Performance status and IPI score varied, and both studies included patients who were fitter in one cohort than the other.

The study authors concluded that the frequency of severe toxicity and increased morbidity required careful attention for high-risk patients,[49] and that although older patients had outcomes comparable to younger patients, objective standards are required when selecting older patients in order to avoid physician bias.[50]

8.1.2 Indolent disease

One study[51] focussed on patients with FL. The study was a multicentre study conducted in Italy between 2004 and 2007. The patients enrolled were aged ≥60 years and had predominantly stage IV disease. Patients were given R-FND (rituximab, fludaribine, mitoxantrone and dexamethasone), and

then either maintenance rituximab or observation. The study reported data on 234 patients with a median age of 66 years (60-75) who had a predominantly high FLIPI score.

The study authors[51] concluded that older patients achieve good outcomes for CR and PFS.

8.1.3 Mixed or undefined disease

One study[52] enrolled populations of patients with mixed or undefined disease. The study focussed on first-line treatment, and was a single-centre study. The study[52] was a phase I/II study conducted in France, and was funded by Schering AG. A total of 23 patients were enrolled to one of four dose-ranging treatment arms with altered doses of F-CVP (fludarabine phosphate, cyclophosphamide, vincristine and prednisone).

Soubeyran et al[52] included a wide mix of subtypes, but predominantly included patients with FL. The majority of patients had stage IV disease, generally with a good PS. Older was defined as >60 years.

The study authors[52] concluded that the regimens used are safe, effective and tolerable for older patients.

Table 10 Study characteristics, comparative cohorts

Study	Details	Population	Intervention	Baseline	Outcomes	Conclusions
NHL – Aggressive disease						
Tholstrup 2007[49]	Single centre Denmark Follow-up 39 months 2002-2003 Funding: Danish Cancer Society; University of Copenhagen	Very high risk DLBCL=91.7% First-line 60-75 years + PS 4, or >75 Stage: I=4.2%; II=12.5%; III=37.5% IV=45.8%	CHOP-14 Very high-risk patients (n=24)	Median age: 76 years (64-83) WHO PS: 0=12.5%; 1=16.7%; 2=25.0%; 3=29.2%; 4=16.7% IPI: L=4.2%; LI-HI=29.2%; H=66.7%	Feasibility, efficacy and safety	Although the 3-year OS in very high-risk DLBCL is encouraging, the high frequency of severe toxicity with infections and malnutrition responsible for increased morbidity during treatment warrants for careful attention to these very high-risk patients
		Standard risk DLBCL=82.9% First-line 60-75 + PS <3, or <60 Stage: I=14.6%; II=29.3%; III=22.0%; IV=34.1%	CHOP-14 Standard-risk patients (n=41)	Median age: 59 years (26-73) WHO PS: 0=48.8%; 1=22.0%; 2=17.1%; 3=9.8%; 4=2.4% IPI: L=14.6%; LI-HI=58.5%; H=9.8%		
Lee 2003[50]	Korea 1994-2000	DLBCL >60=36%	CHOP (N=99, >60 n=52)	>60: Median age: 69 years (60-85) Male: 57% Stage I-II=51% PS 0-1=64% <60: Median age: 47 (60-85) Male: 62% Stage I-II=58% PS 0-1=18%	OS, toxicity	Elderly patients with DLBCL who received doxorubicin at dose intensities ≥10 mg/m^2 per week had treatment outcomes that were comparable to those of young patients; however, physician bias associated with patient age was found to be related to unnecessary dose reductions. Efforts to maintain doxorubicin dose intensities 10 mg/m^2 per week and more objective standards for the selection of elderly patients capable of tolerating doxorubicin-based regimens are required
			COPBLAM-V (N=96, >60 n=18)			

Study	Details	Population	Intervention	Baseline	Outcomes	Conclusions
NHL – Indolent						
Vitolo 2011[51]	Multicentre Italy Follow-up 33 months 2004-2007	FL First-line ≥60 Stage: II=14%; III=21%; IV=65% Overall N=234	R-FND then rituximab R-FND then observation	Median age: 66 years (60-75) FLIPI: L=11%; I=34%; H=55%	Efficacy and safety	A short-term chemo-immunotherapy R-FND + rituximab consolidation is able to achieve high CR rate and a good 2-year PFS in elderly FL patients. Good results were also observed in high-risk FLIPI score
NHL – Mixed or undefined						
Soubeyran 2005[52]	Phase I/II Single centre France Follow-up 68.8 months (58.1-79.5) Funding: Schering AG, France	FL=43%; MCL=35%; SLL=13%; MALT=4.5%; Indolent (unspecified)=4.5% First-line >60 Ann Arbor stage: III=26%; IV=74%	F-CVP (dose 1: low F, low CV) (n=4) F-CVP (2A: high F, low CV) (n=8) F-CVP (2B: low F, high CV) (n=4) F-CVP (3: high F, high CV) (n=7)	Median age: 68 years (61-76) Male:44% WHO PS: 0-2=91%; ≥2=9% FLIPI: L=0; I=30%; H=70%	Safety, efficacy	The study shows that this combination therapy is highly effective. The addition of F to CVP at dose level 2A was feasible and increased the CR rate, with good tolerability in elderly patients

DLBLC=diffuse large B-cell lymphoma; FL=follicular lymphoma; MALT=mucosa-associated lymphoid tissue; MCL=mantle cell lymphoma; NHL=non-Hodgkin's lymphoma; SLL=small lymphocytic lymphoma; PS=performance status; WHO=World Health Organisation; IPI=International Prognostic Index; L=low risk; LI=low-to-intermediate risk; HI=high-to-intermediate risk; H=high risk; FLIPI=Follicular lymphoma International Prognostic Index; PFS=progression-free survival; CR=complete response; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; COPLAM-V=cyclophosphamide, vincristine, bleomycin, doxorubicin, procarbazine, and prednisone; F-CVP=fludarabine phosphate, cyclophosphamide, vincristine and prednisone; R-FND=rituximab, fludarabine, mitoxantrone, dexamethasone

8.2 Efficacy evidence

All studies[49-52] reported efficacy outcomes of interest. Details are presented in Table 11. There were a range of outcomes reported across studies, including: 3-year EFS,[49] PFS,[51] 3-year OS,[49,52] 5-year survival,[50] 2-year OS,[51] median OS,[52] and ORR.[51,52]

8.2.1 Aggressive disease

Tholstrup et al[49] reported results for high-risk versus standard-risk patients treated with CHOP, and 3-year EFS was higher for standard risk patients; however, the result was not statistically significant (52% vs 40%; p=0.203). In terms of 3-year OS, the result for standard-risk patients was statistically significant: 68% versus 44% (p=0.017). Lee et al[50] reported that 5-year survival rates were higher for patients aged <60 years (57%) on any dose of CHOP or COPBLAM-V than older patients (30%; p<0.001).

8.2.2 Indolent disease

Vitolo et al[51] reported that 2-year PFS was higher for patients who received maintenance rituximab, compared with those undergoing observation, but the result was not statistically significant (80% vs 68%; p=0.225). For all patients, 2-year OS was 93% (95% CI 92-97). For all patients, ORR was 86%.

8.2.3 Mixed or undefined disease

Soubeyran et al[52] reported outcomes for median OS (70.3 months) and 3-year OS (65%±10%) for all patients receiving F-CVP. The reported ORR was 78% for all patients.

Table 11 Survival outcomes, comparative studies

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
NHL – Aggressive disease							
Tholstrup 2007[49]	CHOP-14 Very high risk	3-year EFS=40%	p=0.203	3-year OS=44%	p=0.017	NR	NR
	CHOP-14 Standard risk	3-year EFS=52%		3-year OS=68%			
Lee 2003[50]	CHOP or COPBLAM-V <60 (any dose)	NR	NR	5-year survival=57% OS=not reached	p<0.001	NR	NR
	≥60 (any dose)			5-year survival=30% OS=29 months			
	≥60 with ≥10 mg/m² per week (25 patients)			5-year survival=52% OS not reached	p=0.039		
	≥60 with <10 mg/m² per week (45 patients)			5-year survival=18% OS=23 months			
	60-64 (original 211 patients)			OS=30 months	p=0.001		
	65-69 (original 211 patients)			OS=23 months			
	≥70 (original 211 patients)			OS=23 months			
NHL – Indolent							
Vitolo 2011[51]	All patients	2-year PFS=77% (71-93)	NR	2-year OS=93% (92-97)	NR	86%	NR
	Rituximab maintenance	2-year PFS=80%	p=0.225	NR	NR	NR	NR
	Observation	2-year PFS=68%		NR	NR	NR	NR
NHL – Mixed or undefined							
Soubeyran 2005[52]	F-CVP – all doses	NR	NR	Median OS=70.3 months 3-year OS=65%±10%	NR	78%	NR

EFS=events-free survival; PFS=profression-free survival; TTP=time to progression; OS=overall survival; ORR=overall response rate; CI=confidence interval; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; COPBLAM-V=cyclophosphamide, vincristine, bleomycin, doxorubicin, procarbazine, and prednisone;F-CVP=fludarabine phosphate, cyclophosphamide, vincristine and prednisone; NR=not reported

8.3 Tolerability evidence

Four studies[49-52] reported outcomes relating to tolerability. Details are presented in Table 12.

8.3.1 Aggressive disease

Tholstrup et al[49] and Lee et al[49,50] reported a limited number of outcomes relating to tolerability. Discontinuations were reported by Tholstrup et al,[49] who reported that there were higher rates of discontinuations due to toxicity or progression for high-risk patients (33%) than standard-risk patients (12%). Delays were also higher in the high-risk group (92%) compared with 80% in the standard-risk group receiving CHOP.[49]

Grade 3-4 AEs were well reported by Tholstrup et al[49], with higher-risk patients experiencing much higher rates across all AEs reported, with the exception of neuropathy, which was higher in the standard-risk group. Lee et al[50] reported rates of leukopenia between older and younger patients receiving any dose of CHOP or COPBLAM-V, and the results were similar (30% and 34%).

8.3.2 Indolent disease

Vitolo et al[51] reported information relating to treatment discontinuations for the whole study population, with progressive disease and AEs being the most common reason for discontinuation. It was reported that 25% of courses had grade 3-4 neutropenia.

8.3.3 Mixed or undefined disease

Soubeyran et al[52] reported information relating to the different dosing schedules of patients treated with F-CVP. The discontinuations are hard to compare as they happened at different points throughout treatment, but they varied from 12.5% to 50%. Across all arms, dose reductions were high (above 75%). The number of grade 3-4 AEs were found in 38%, 44%, 11% and 27% of cycles across the four dosing regimens.

Table 12 Tolerability, comparative studies

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
NHL – Aggressive disease				
Tholstrup 2007[49]	NR	CHOP high risk Discontinuation=33%, due to toxicity, progression and death	Delays in 92% of patients Median delay=14 days (range 0-67)	Grade 3-4 AEs: Febrile neutropenia=58.3% Mucositis=25% Neuropathy=4.2% Fatigue=66.7% Weight loss=12.5%
	NR	R-CHOP standard risk Discontinuation=12%, due to toxicity, progression and death	Delays in 80% of patients Median delay=8 days (0-44)	Grade 3-4 AEs: Febrile neutropenia=22% Mucositis=4.9% Neuropathy=14.6% Fatigue=14.6% Weight loss=2.4.5%
Lee 2003[50]	NR	NR	NR	CHOP or COPBLAM-V <60 (any dose): Grade 3-4 leukopenia=34% Treatment-related deaths=4 patients
	NR	NR	NR	CHOP or COPBLAM-V ≥60 (any dose): Grade 3-4 leukopenia=30% Treatment-related deaths=4 patients
	NR	NR	NR	≥60 with ≥10 mg/m² per week (25 patients) NR
	NR	NR	Dose reduction=8.6%, due to AEs after initial full dose Initial dose reduction=55.7% (of all patients ≥60), due to: Poor PS=14 patients Comorbidities=5 patients Old age=20 patients (despite PS ≤1 and no comorbidities)	≥60 with <10 mg/m² per week (45 patients) NR
NHL – Indolent				
Vitolo 2011[51]	NR	Rituximab maintenance or observation	NR	Grade 3-4 neutropenia=25% of courses

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		Discontinuation: Progressive disease=15 patients AEs=9 patients Other=8 patients Toxic deaths=2 patients (0.8%)		(<10% of grade 3-4 toxicities occurred during consolidation)
NHL – Mixed or undefined				
Soubeyran 2005[52]	NR	F-CVP dose level 1 (4 patients): Discontinuations=2 patients (50%); after cycle 4 & 6 Deaths=2 patients	Dose reductions=5 cycles in 4 patients (100%); Cycle 3-7=1 patient per cycle (25%)	Any grade 3-4 AEs=38% of cycles Grade 3-4 AEs (of patients): Neutropenia=75% Infection=0 Thrombocytopenia=0 Mucositis=0 Cerebral toxicity=0
	NR	Dose level 2A (8 patients) Discontinuations=1 patient (12.5%); after cycle 6 Deaths=3 patients	Dose reductions=27 cycles in 7 patients (87.5%); Cycle 2=2 patients (25%) Cycle 3-4=3 patients (37.5%) Cycle 5=4 patients (50%) Cycle 6=5 patients (62.5%) Cycle 7-8=5 patients (71.4%)	Any grade 3-4 AEs=44% of cycles Grade 3-4 AEs (of patients): Neutropenia=87.5% Infection=12.5% Thrombocytopenia=12.5% Mucositis=0 Cerebral toxicity=0
	NR	Dose level 2B (4 patients) Discontinuations=1 patient (25%); after cycle 5 Deaths=2 patients	Dose reductions=4 cycles in 3 patients (75%); Cycle 2 & 5=1 patient (25%) Cycle 8=2 patients (50%)	Any grade 3-4 AEs=11% of cycles Grade 3-4 AEs (of patients): Neutropenia=75% Infection=25% Thrombocytopenia=75% Mucositis=0 Cerebral toxicity=0
	NR	Dose level 3 (7 patients) Discontinuations=1 patient (14.3%); after cycle 4 Deaths=4 patients	Dose reductions=30 cycles in 7 patients (100%); Cycle 2=3 patients (42.9%) Cycle 3-4=4 patients (57.1%) Cycle 5-6=5 patients (83.3%) Cycle 7=4 patients (57%) Cycle 8=5 patients (83.3%)	Any grade 3-4 AEs=27% of cycles Grade 3-4 AEs (of patients): Neutropenia=71% Infection=28.5% Thrombocytopenia=0 Mucositis=28.5% Cerebral toxicity=14%

NHL=non-Hodgkin's lymphoma; AE=adverse event; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; COPBLAM-V=cyclophosphamide, vincristine, bleomycin, doxorubicin, procarbazine and prednisone; F-CVP=fludarabine phosphate, cyclophosphamide, vincristine and prednisone; NR=not reported

8.4 Geriatric assessment and quality of life

Only one study[51] reported outcomes relating to CGA. See Table 13 for details.

Vitolo et al[51] used an unspecified CGA tool to measure concomitant illnesses among patients at baseline.

Table 13 Comprehensive geriatric assessment and quality of life, comparative studies

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
Vitolo 2011[51]	Unspecified CGA	To measure concomitant illness at baseline (1=38%, ≥2=23%)	NR	NR

CGA=comprehensive geriatric assessment; NR=nor reported

8.5 Summary and discussion

Four studies[49-52] that compared two or more non-randomised treatment arms were included in the review. Two studies[49,50] focussed on patients with aggressive disease, one study[51] focussed on patients with indolent disease, and one study[52] focussed on mixed or undefined populations.

Studies were generally small, single-centre studies, and populations were heterogeneous. A variety of treatment regimens were used across studies, including CHOP, COPBLAM-V, R-FND, and F-CVP. Efficacy and tolerability outcomes were poorly and inconsistently reported, which makes both synthesis and translation of evidence particularly problematic. Only one study presented limited data relating to CGA.

Study authors' conclusions generally suggest that older patients have outcomes comparable to younger patients, and that the regimens used are safe, effective, and tolerable for fit older patients. However, the frequency of severe toxicity and increased morbidity means that careful attention is required in high-risk patients.

9 SINGLE COHORTS

Sixty-three single cohort studies[53-115] (reported in 70 publications[53-122]) were included in the review. Study characteristics are presented in Table 14.

9.1 Study characteristics

Fifty single-cohort studies[53-102] focussed on patients with aggressive disease, eight single-cohort studies[103-110] focussed on patients with predominantly indolent disease, and five of the single cohort studies[111-115] included a mixed or undefined patient population. Some of the studies enrolled only older patients, whereas others report data for both older and younger patients.

9.1.1 Aggressive disease

Fifty studies[53-102] had a patient population reported as having aggressive disease. Where data were reported regarding study characteristics, 29[54,56-58,62-66,69,71,72,76,77,80,82,85,87-91,93,94,96,98-101] of the studies were phase II clinical trials, two studies[59,74] were phase I/II, and one was a pilot study.[79] Fifteen[53-56,62,72,75,81-83,86,88,95,99,101] were single-centre studies, and 21 studies[58,64,65,68-71,76-78,80,84,85,87,89,91,94,96-98,100] were multicentre. The majority of studies that reported study location were conducted in Europe, with nine studies conducted in Asia,[53,57,65,68,81,82,87,88,92] eight studies[59,69,70,72,73,89,93,96,102] were conducted in the USA, and two studies[77,84] were conducted in Australia. Eight studies[56,63,69,71,83,84,96,100] reported the funding source as a pharmaceutical company, and six studies[58,62,64,69,70,78] were funded by research grants.

In terms of study populations, where specifically reported, the main subtype of NHL was DLBCL, or mixed aggressive subtypes. The exceptions were Illerhaus et al,[76] which enrolled patients with primary central nervous system lymphoma (PCNSL), and Niitsu et al,[82] which included peripheral T-cell lymphoma (PTCL). The majority of studies did not report the line of treatment, or reported the study as first line. The mix of disease stages (where reported) across studies varied greatly, as did the age cut-off for 'older'. Over 60% of the studies used >60 or >70 as the age cut-off for inclusion to the study, six studies[54,75,76,87,88,102] used >65, two studies[63,64] used >80, Vacirca et al[73] used >54, and Faveau et al[74] included patients aged 60-80 years.

9.1.2 Indolent disease

Eight studies[103-110] focussed on patients with predominantly indolent disease. Where reported, five studies[103,104,107,109,110] were phase II trials, and one study[105] was a phase I trial. Four studies[103,104,106,109] were multicentre. Funding was reported in four studies: two studies[103,107] was supported by research grants, and two studies[108,109] were supported by pharmaceutical companies. Six studies[103-106,108,110] were conducted in Europe, and two studies[107,109] were conducted in the USA.

The studies were primarily concerned with patients who had mantle cell lymphoma (MCL) and, where reported, the studies were first-line, with the exception of Ruan et al.[107] The cut-off age for inclusion was >60/>65 years, apart from Ruan et al,[107] which included patients aged >50 years.

9.1.3 Mixed or undefined disease

Five studies[111-115] included a mixed subtype or undefined patient population. Study characteristics were not well reported. Three of the studies[111,113,115] were singe centre, and two studies[112,114] were multicentre. Two studies[112,114] that reported the trial phase, were phase II. Only two studies[112,113] reported the funding source, both of which were supported by research grants. Three studies[111,113,115] were conducted in Europe, one study[112] in Japan, and one study[114] was conducted in the USA.

Table 14 Study characteristics, single cohorts

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
NHL – Aggressive disease						
Shin 2012[53]	Single centre Korea 2004-2009 Follow-up 30 months (range 1-71)	DLBCL Ann Arbor: I=24.7% II=45.9% III=16.5% IV=12.9% Aged ≥60 (>69=48.2%; ≥75=20%)	Reduced-dose R-CHOP (n=85)	Median age: 69 years (61-85) Male: 52.9% PS: 0=43.5% 1=30.6% 2=8.2% 3=17.6% IPI: L=29.4% LI=35.3% HI=22.4% (aaIPI=23.5%) H=21.9% (Age-adjusted=11.8%)	The aim of this study was to evaluate the efficacy and toxicity of reduced-dose R-CHOP chemotherapy without G-CSF prophylaxis in DLBCL patients aged >60	Reduced-dose R-CHOP chemotherapy is well tolerated and effective in elderly patients with DLBCL
Boccomini 2012[54] (abstract only)	Phase II Single centre Italy 2009-2011	Advanced follicular BCL +ve=58% Stage II=19%, III=27%, IV=54% First-line Aged >65	R-BM followed by rituximab consolidation (n=69)	Median age: 71 years (65-80) Male: 38% WHO PS: I=16%; II=55%; IIIa=29% FLIPI: Low=12% Intermediate=30% High=58%	To investigate safety and efficacy of a similar combined brief regimen substituting bendamustine for fludarabine aimed at reducing toxicity and maintaining efficacy	A brief course of chemo-immunotherapy R-BM followed by rituximab consolidation is safe and effective with a high CR rate in elderly patients with untreated advanced-stage FL. Planned future analysis of the entire study will give further information
Chaibi 2012[55] (abstract only)	Single centre France Follow-up 18 months 2008-2011	DLBCL Aged >70 (≥80=84%, ≥90=16%)	R-mini-CHOP (n=74)	Median age: 84 years (71-97) Male: 32 PS: 2=67.5% aaIPI: L-LI=12% HI=38% H=47%	NR	In unselected elderly patients with DLBCL, immunochemotherapy with R-mini-CHOP can be effective, but with significant toxicity, even using systematic G-CSF prophylaxis. Prognosis remains poor for patients with aaIPI 3
Chiappella 2012[56]	Phase II Single centre	DLBCL Stage III/IV=88%	Lenalidomide + R-CHOP-21	Median age: 69 years (61-80)	To evaluate toxicity and activity of lenalidomide	The addition of 15 mg lenalidomide on days 1–14 to

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
(abstract only)	Italy Follow-up 18 months 2010-2011 Funding: partially supported by Celgene	First-line Aged >60	(n=49)	PS: 1=63% IPI: IH/H=61%	plus R-CHOP-21 in elderly untreated DLBCL	R-CHOP-21 is safe, feasible and effective in elderly untreated DLBCL
Fan 2012[57] (abstract only)	Phase II China Follow-up 7 months (4-26) 2010-2012	DLBCL First-line Aged ≥70 (≥60 with PS ≥2) (<70=25%)	R-GemOx (n=12)	Median age: 73 years (61-85) Male: 41.7% ECOG PS: ≥2=92% IPI: L=0 LI=33.3% HI=16.6% H=50%	NR	This is the first clinical study to investigate the safety and efficacy of R-GemOx regimen in elderly patients with DLBCL. Rituximab combined with GemOx appears highly active and favourable toxicity profiles in elderly patients with DLBCL requiring treatment
Spina 2012[58]	Phase II Multicentre Italy Follow-up 64 months (1-127) 2000-2006 Funding: Alleanza Contro il Cancro	DLBCL Ann Arbor: I-II=49% III-IV=51% First-line Aged ≥70	R-CHOP or varients; CEOP, CVP, CHO or CHP (all ±R) (n=100)	Median age: 75 years (70-89) Male: 41%	To evaluate the feasibility and efficacy of chemotherapy modulated according to a modified CGA in patients aged >70 years with DLBCL	Chemoimmunotherapy adjustments based on a CGA are associated with manageable toxicity and excellent outcomes in elderly patients with DLBCL. Wide use of this CGA-driven treatment may result in better cure rates, especially in fit and unfit patients
Straus 2012[59] (abstract only)	Phase I/II USA Follow-up 9.2 months	DLBCL Second-line Aged >60	R-CVEP (n=26)	Median age: 76 years (69-88) Male: 46% ECOG PS: Median=1 (0-2)	This trial defined the maximum tolerated dose of vorinostat added to standard therapy and determined the response rate of this combination	The ORR rate for vorinostat added to conventional chemotherapy and rituximab was 55% (CR 30%, PR 25%) in relapsed/refractory DLBCL in elderly patients not candidates for autologous stem cell transplantation. This could provide a baseline for comparison with future trials in this understudied population
Rodriguez	NR	DLBCL	DRCOP	Median age: 71 years	NR	DRCOP is an active regimen.

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
2011[60] (abstract only)		First-line Aged >60 Stage II to IV	(n=80)	Male: 50%		In this study of older patients with DLBCL, only one patient had drop in left ventricular ejection fraction below normal. Other cardiac events were associated with underlying cardiac conditions, and were reversible. Liposomal doxorubicin should be considered in older patients. Co-management by a cardiologist during chemotherapy would be recommended
Musolino 2011[61]	Italy Follow-up 22 months (3-46+) 2006-2009	DLBCL Ann Arbor II=17% III-IV=83% First-line Aged ≥70 (>80=43%)	DA-POCH-R (n=23) (21 evaluable)	Median age: 77 years (70-90) Male: 30% PS by group=ECOG <2=26% ≥2=74% aaIPI: I=57% H=43%	To assess the activity and safety of DA-POCH-R in elderly patients with poor-prognostic untreated DLBCL	DA-POCH-R was an active and safe combination therapy for patients aged ≥70 years with poor-prognostic untreated DLBCL. This regimen was a reasonable alternative for elderly patients who were not considered to tolerate standard R-CHOP treatment
Zinzani 2011[62]	Phase II Single centre Italy Follow-up 16 months (12-18) March-June 2009 Funding: Italian Association for Leukemias, Lymphomas, and Myeloma	DLBCL Ann Arbor II=22% III=26% IV=52% Second-line Median number of prior therapies=3 (2-8) Aged ≥65	Lenalidomide plus rituximab (n=23)	Median age: 74.2±9.9 years Male: 52.2% PS by group= IPI=L=4% LI=26% HI=52% H=17%	To evaluate the safety and efficacy of lenalidomide plus rituximab in elderly patients with relapsed or refractory DLBCL	Oral lenalidomide in combination with rituximab is active in elderly patients with relapsed/refractory DLBCL with a high percentage of patients achieving a continuous CR after lenalidomide maintenance
Weidmann 2011[63]	Phase II Germany Follow-up 54.5 months (20-72)	Aggressive Stage: I=43% II=14%	Bendamustine plus rituximab (n=14) (13 assessable)	Median age: 85 years (80-95) Male: 64% aaIPI:	To determine whether this combination was suitable for patients with aggressive B-cell	Because of its efficacy and low toxicity, bendamustine in combination with rituximab may be an alternative

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
	2004-2006 Funding: Roche and Ribospharm/Mundipharma	III=21.5% IV=21.5% First-line Aged ≥80		L=36% LI=21% HI=43%	lymphomas, who did not qualify for combinations of rituximab with CHOP-like regimens	treatment for aggressive lymphomas in old patients not eligible for R-CHOP. These results, however, need to be confirmed in larger studies
Peyrade 2011[64]	Phase II Multicentre France, Belgium Follow-up 20 months (0-45) 2006-2009 Funding: GELA, Roche	DLBCL Ann Arbor: I=9% II=16% III=23% IV=52% First-line Aged >80	R-mini-CHOP (n=150) (149 ITT)	Median age: 83 years (80-95) Male: 34 PS: 0=18% 1=48% 2=34%	To assess the efficacy and safety of the combination of a standard dose of rituximab and an attenuated dose of chemotherapy in this patient population	R-mini-CHOP offers a good compromise between efficacy and safety in patients aged >80 years. R-mini-CHOP should be considered as the new standard treatment in this subgroup of patients
Kasahara 2011[65]	Phase II Multicentre Japan Follow-up 44.4 months 2003-2005	DLBCL Stage: I-II=42% III-IV=58% First-line Aged ≥70 (>75=40%)	R-THP-COP (n=52)	Median age: (70-80) Male: 58% PS: 0-1=63% 3-4=37% IPI: L-LI=40% HI-H=60%	To assess the response rates, long-term effects, and toxicity of the R-THP-COP regimen as first-line treatment for previously untreated elderly patients with CD20þ DLBCL and evaluated its clinical effects	We conclude that the R-THP-COP regimen is safe and effective for patients with DLBCL. Based on these results, an RCT of R-CHOP and R-THP-COP as a phase III study is ongoing
Corazzelli 2011[66] (abstract only)	Phase II Italy Median observation for TTF=27months 2007-2009	DLBCL Stage: II=10% III=24% IV=66% First-line Aged >60 (>75=36%)	R-COMP-14 (n=41)	Median age: 73 years (62-82) Male: 56% ECOG PS: >=2=32% IPI: 3=59% 4-5=41%	NR	R-COMP-14 is feasible and ensures a substantial DFS to poor-risk DLBCL patients who would have been denied anthracycline-based treatment due to cardiac morbidity. The aaCCI predicted both treatment discontinuation rate and TTF
Boggiani 2010[67] (abstract only)	Italy 2006-2009	DLBCL Ann Arbor: III-IV=83% First-line Aged >70	Dose-adjusted POCH-R (n=23)	Median age: 77 years (70-90) IPI=100% 2 or 3 (aaIPI)	NR	Dose-adjusted POCH-R is an active and safe combination therapy for patients aged >70 years with poor-prognostic untreated DLBCL. This regimen is a reasonable

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
						alternative for elderly patients who are not considered to tolerate standard R-CHOP treatment
Ishii 2010[68]	Multicentre Japan Follow-up 24.4 months 2004-2007	DLBCL=95.6% MLBCL=4.4% Ann Arbor; I-II=26.1% III-IV=73.9% First-line Aged ≥60 (≥70=87%; ≥75=43.5%; ≥80=17.4%)	R-VNCOP-B (n=23) (21 evaluated)	Median age: 73 years (68-85) Male: 43.5% PS: 0-1=87% 2-3=13% Standard and age adjusted IPI: L-LI=50% HI-H=50%	To address the questions whether VNCOP-B plus rituximab was effective and safe to treat previously untreated elderly patients with aggressive NHL	Although the trial was carried out on a small number of patients, our outcome was not inferior to R-CHOP or other regimen in elderly patients without remarkably increased treatment-related toxicity. Larger RCTs comparing R-CHOP and R-VNCOP-B are warranted
Hainsworth 2010[69]	Phase II Multicentre US Follow-up 48 months 2003-2007 Funding: Genentech, Amgen and the Minnie Pearl Cancer Foundation	DLBCL Ann Arbor II=20% III=47% IV=33% Aged >60 (>80=43%)	R-CNOP [73%] or R-CVP (n=51)	Median age: 78 years (61-90) Male: 29% PS by group=ECOG 0=20% 1=43% 2=37% IPI: L=8% LI=20% HI=37% H=35%	To evaluate a novel regimen for the first-line treatment of patients with DLBCL who were not considered candidates for full-course R-CHOP chemotherapy	This abbreviated course of rituximab/chemotherapy, followed by maintenance rituximab, was active and well tolerated in these very elderly patients. Brief-duration rituximab/chemotherapy as well as maintenance rituximab merit further evaluation in this set
Chang 2010[70]	Multicentre USA Follow-up 51.1 months 2002-2005 Berlex Oncology, Academic Oncologist K12 Training Grant, Cancer Center Support Grant	DLBCL Stage: I-II=16% III=32% IV=53% First-line Aged >60	R-CHOP plus GM-CSF (n=38)	Median age: 72 years (62-86) Male: 58 PS: 0=26% 1=47% 2=26% IPI: L=8% LI-HI=63% H=29%	To evaluate the tolerability and efficacy of GM-CSF combined with standard R-CHOP in an elderly population of patients with newly diagnosed DLBCL	These data suggest that survival outcomes may be modestly improved when GM-CSF is combined with R-CHOP in the treatment of elderly DLBCL. GM-CSF had toxicity precluding planned administration in 16% of patients, which may limit usefulness of this agent
Luminari 2010 [71]	Phase II Multicentre	DLBCL I-II=31%	R-COMP (NPLD) (n=72)	Median age: 72 years (61-83)	To assess the activity and safety of NPLD in	R-COMP is an effective regimen for the treatment of

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
	Spain, Italy, UK, Germany & France Follow-up 33 months (1-72) 2002-2005 Funding: Cephalon Inc.	III-IV=69% First-line Aged >60 (≥70=60%)		Male: 44 ECOG PS: 0-1=82% >1=18% IPI: L=21% LI=23% HI-H=56%	combination with R-COMP for the initial treatment of elderly patients with DLBCL	DLBCL in elderly patients, with an acceptable tolerability profile
Noga 2010[72] (abstract only)	Phase II Single centre USA	DLBCL Aged >60 (≥70=71%, ≥80=47%)	R-CHOP (n=17) (15 for analysis)	Median age: 78 years (62-87) Male: 41%	NR	It is feasible to deliver a dose-dense anthracycline regimen to geriatric patients with acceptable toxicity. Indeed, 71% of study patients were >70 years and 47% were >80 years. Microarray analysis may pinpoint which elderly patients may require a more intensive regimen to effect cure
Vacirca 2010[73] (abstract only)	USA Ongoing	DLBCL Relapsed/refractory Aged ≥54	Bendamustine plus rituximab (n=33)	Median age: 74 years (54-90) ECOG PS: 0=42% 1=53% 2=5% Revised-IPI: Very good/good=30% Poor=70%	NR	Data from our ongoing trial suggest that bendamustine plus rituximab may have a role in the treatment of relapsed/refractory DLBCL, particularly for older patients who are not candidates for transplant and who may not tolerate aggressive therapy associated with higher toxicity
Fauveau 2009[74] (abstract only)	Phase I/II France Follow-up 22 months 2003-2008	Aggressive III-IV First-line Aged 60-80	Idarubicin in combination with oral cyclophosphamide, etoposide, prednisolone and intravenous rituximab (n=19)	Median age: 70 years (62-80)	NR	This first analysis clearly shows that the maximum tolerated dose of oral idarubicin administrated with cyclophosphamide, etoposide, prednisolone and rituximab is 40 mg/m^2 on day 1 every 21-day cycle. The recommended dose study is ongoing

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
Tucci 2009[75]	Single centre Italy 2003-2006	DLBCL Stage III-IV: Fit=66% Unfit=64% Aged >65 (≥70=61%)	CHOP or CHOP-like therapy/palliative therapy (n=84)	Median age: 73 years (66-89) Fit=52% Unfit=29% IPI: HI-H; Fit=57% Unfit=69%	To objectively evaluate the potential usefulness of CGA categorisation as a predictor of treatment tolerability and outcome	CGA is an efficient method to identify elderly DLBCL patients who can benefit from a curative approach with anthracycline-containing immunochemotherapy. Further study is needed to discern why unfit patients seem to have poor outcomes because of poor tolerance
Illerhaus 2009[76]	Phase II Multicentre Germany Follow-up 78 (34-105) 1998-2004	PCNSL=97% Intraocular=3% First-line Aged >65 (>65=90%)	Methotrexate, procarbazine + CCNU (n=30) (27 assessable for response)	Median age: 70 years (57-79) Male: 50% KPS: median=60% (30-90); KPS >70%=33%, <70%=77%	NR	The combination of high-dose methotrexate with procarbazine and CCNU is feasible and effective and results in a low rate of leukoencephalopathy. Comorbidity and toxicity remain of concern when treating PCNSL in elderly patients
Mitchell 2008[77]	Phase II Multicentre Australia	Aggressive: DLBCL=94% FL=4% T-cell=2% I=12% II=24% III=43% IV=21% First-line Aged ≥60 (≥70=57%)	COP-X (n=51) (46 evaluable for efficacy)	Median age: 70 years (60-88) Male: 53% PS: 0=39% 1=37% 2=24% aaIPI: L=8% LI=37% IH=33% H=22%	To assess the response rate of liposomal daunorubicin, given in combination with cyclophosphamide, vincristine and prednisolone as first-line treatment of elderly patients with aggressive lymphoma	The high rate of infectious complications suggests that the liposomal daunorubicin dose used may be too high for this patient group. These results support further investigation of this regimen in patients with aggressive NHL
Zwick 2008[78]	Multicentre Germany Funding: Deutsche Krebshilfe	Aggressive Stage: I=6%; II=23%; III=51%; IV=19% Aged>60 (>60=92%)	CEMP (n=47)	Median age: 68 years (40-75) Male: 62% ECOG PS >1: 34% IPI: LI=35%; HI=30%;	To compare differences in the course of leukocytopenia and thrombocytopenia between the two application schedules	The observed equitoxicity and the more challenging logistics of a 60-hour infusion make bolus injection the preferred application of etoposide. As the CEMP regimen is well tolerated and efficacious in elderly patients

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
				H=17%		with relapsed or refractory aggressive NHL
Isidori 2007[79] (abstract only)	Pilot Italy Follow-up14 months (7-18)	DLBCL First-line=75% Aged >60 Stage III/IV=72%	R-COMP-21 (n=20)	Median age: 73 years (61-82) IPI: HI-H=90%	NR	The R-COMP-21 is a very effective regimen with promising response rates in frail and elderly patients with high-risk aggressive NHL. Further studies with a larger cohort of patients are warranted to better define the impact of NPLD on OS of this setting of elderly and particularly frail patients
Mey 2007[80]	Phase II Multicentre Germany 2004-2005	DLBCL First-line Aged ≥60	R-CHOP-14 with pegfilgrastim (n=10)	Median age: 73.4 years (59-80) Male: 70%	To evaluate the feasibility, toxicity and pharmacokinetics of the R-CHOP-14 regimen supported by pegfilgrastim	A single fixed dose of 6 mg of pegfilgrastim given once per cycle of R-CHOP-14 is effective in supporting neutrophil recovery to allow 2-weekly drug administration in previously untreated elderly patients with DLBCL. However, close monitoring for infectious complications is mandatory in this patient population
Tsurumi 2007[81]	Single centre Japan Follow-up 48 months 1993-2002	DLBCL Stage: II=23% III-IV=77% First-line Aged ≥70	THP-COP 70-79, n=45 THP-COP ≥80, n=16	Median age: 76 (70-92) 73 (70-79) / 83 (80-92) Male: 55% PS: 0-1=62% 2-3=38% IPI: L-LI=34% HI-H=66%	To assess the efficacy of THP-COP therapy for the treatment of previously untreated DLBCL in patients aged ≥70 years, including those with concurrent diseases	The present findings indicate the necessity of future studies investigating a combination therapy comprised of rituximab and THP-COP for the treatment of elderly patients with CD20-positive DLBCL
Niitsu 2007[82]	Phase II Single centre Japan Follow-up 32 months 2001-2005	PTCL II=23.3% III=43.3% IV=33.3% Relapsed=83.3% or refractory=16.7%	CMD (n=30)	Median age: 75 years (70-79) Male: 53.3%	To study the safety and efficacy of CMD in an elderly population	Results indicate the CMD regimen is safe in elderly patients and no cardiotoxicities developed as a result of this regimen. It was effective in patients who

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
		Aged ≥70				had previously been treated with doxorubicin and good treatment results were obtained in elderly patients with relapsed PTCL
Fina 2007[83]	Single centre Italy Follow-up 24 months (12-42) 2003-2005 Funding: BolognAIL	DLBCL Stage: II=21% III=21% IV=58% First-line Aged ≥60	R-VNCOP-B (n=24)	Median age: 67 years (60-79) Male: 50% IPI: L=25% LI-H=75%	To evaluate the efficacy of R-VNCOP-B	This regimen was effective in inducing a good remission rate with moderate toxic effects in elderly DLBCL patients
Wolf 2006[84]	Multicentre Australia 2002-2003 Funding: Amgen Australia Pty Ltd	Aggressive: DLBCL=97%; AILT=3% First-line Aged ≥60 Stage: I=13%; II=17%; III=30%; IV=40%	CHOP-14 (n=30)	Median age: 68 years (61-74) Male: 47% IPI: L=10%; LI=40%; HI=23%; H=27%	To assess the proportion of patients receiving full-dose chemotherapy, the proportion of chemotherapy cycles given at full dose, and disease response	The delivery on schedule of dose-dense CHOP-14 to elderly patients with previously untreated aggressive NHL is safe and efficacious with once per cycle pegfilgrastim support
Zaja 2006[85]	Phase II Multicentre Italy 2002-2004	DLBCL I=7% II=28% III=31% IV=34% First-line=Yes Aged ≥60=100%	Modified R-CHOP (R-CCOP) (n=30) (29 evaluable)	Median age: 69 years (60-75) Male: 55 IPI: L=14% LI=24% HI=38% H=24%	To evaluate the efficacy and tolerability of a pegylated liposomal - doxorubicin modified R-CHOP regimen, applied to a population of elderly patients with DLBCL	This regimen appears an active regimen for the treatment of elderly patients with DLBCL. The replacement of conventional doxorubicin with pegylated liposomal doxorubicin seems to be associated with a negligible incidence of extra-haematological toxicity, in particular cardiac and infectious complications
Rigacci 2006[86]	Single centre Italy 2002-2004	DLBCL Stage: II=27% III-IV=73% First-line Aged ≥60 (≥70=19%)	R-CHOP-14 with G-CSF (n=26)	Median age: 65 years (60-76) Male: 65 IPI: LI=31% HI-H=69%	To verify the feasibility of this scheme in a subset of patients with high-risk aggressive lymphomas	These results confirm that a dose-dense CHOP programme can be administered safely and effectively in a subset of elderly patients with high-risk aggressive NHL. The addition

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
						of rituximab could increase the response rate without adding toxicity
Niitsu 2006[87]	Phase II Multicentre Japan Follow 64 months 1998-2003	Aggressive; DLBCL=73% FL=4% PTCL-U=12% T-cell=6% AILT=6% II=12% III=49% IV=39% First-line Aged ≥65	CyclOBEAP (n=51)	Median age: 67 years (65-69) Male: 55% PS: 0-1=82% 2=18% IPI: LI=16% HI=61% H=24%	To investigate the CyclOBEAP-elderly regimen in elderly patients with poor-prognosis aggressive lymphoma	We showed that the CyclOBEAP regimen can be safely used in the treatment of aggressive lymphoma in elderly patients and it achieved a high rate of remission
Niitsu 2006[88]	Phase II Single centre Japan Follow-up 23 months	DLBCL II=23.7% III=46.7% IV=23.7% Relapsed=86.7% Refractory=13.3% Aged ≥65	R-CMD (n=30)	Median age: 73 years (65-79) Male: 60%	To investigate the safety and efficacy of R-CMD	The R-CMD regimen could be used safely in elderly patients and no new signs of cardiotoxicity were found. It was effective for patients with relapsed or refractory DLBCL who were previously treated with doxorubicin. However, further long-term follow-up is needed
Desch 2005[89] (abstract only)	Phase II Multicentre USA	Intermediate or high grade NHL First-line Aged >60 (>60=58%)	R-CHOP maintenance rituximab plus filgrastim (N=101) (older=59)	NR	To determine whether adding filgrastim to R-CHOP in older patients would result in decreased incidence of febrile neutropenia, and allow full doses to be delivered	Patients >60 years receiving R-CHOP with filgrastim achieved a response rate that was similar to younger patients, with a 50% reduction in febrile neutropenia compared to a previously reported phase 3 study (p=0.005) without filgrastim in 1st cycle
Federico 2005[90] (abstract only)	Phase II Italy, UK, Spain, Germany	DLBCL First-line >60% Stage III-IV=56%	R-COMP First stage: n=30 Second stage: n=33	Median age: 72 years (61-82)	NR	These interim results suggest R-COMP is a well-tolerated regimen with promising response rates in elderly patients with advanced DLBCL

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
Monfardini 2005[91]	Phase II Multicentre Italy Follow-up 10.5 months (0.1-44.2) 1999-2003	Aggressive: DLBCL=76.7%; FL=6.7%; MCL=3.3%; PTCL=13.3% First-line Aged ≥70 (≥80=73%) Stage: I=6.7%; II=36.7%; III=26.6%; IV=30.0%	Vinorelbine and prednisone (n=30)	Median age: 83 years (70-96) Male: 33% aaIPI: L=13.3%; LI=30.0%; HI=36.7%; H=20.0%	To evaluate the efficacy and tolerability of vinorelbine and prednisone in frail elderly patients with NHL	Vinorelbine and prednisone is a relatively non-toxic combination with modest activity in frail patients with NHL. If initial aggressive chemotherapy has been excluded, this combination could be tried to obtain a temporary palliation
Goto 2005[92]	Japan 1995-2001	DLBCL=85% PTCL=15% Stage: I/II=19.5% III/IV=80.5% First-line Aged >60 (>60=72%)	THP-COP/CHOP (n=113)	Median age: 66 years (14-92) Male: 61% PS: 0-1=64% 2-4=36% IPI: L/LI=35% HI/H=65%	To assess the prognostic significance of serum soluble interleukin-2 receptor (sIL-2R) in aggressive NHL	The results suggest that a high serum sIL-2R level predicts a poor prognosis in aggressive NHL and may be a useful biomarker for selecting appropriate treatment when used in combination with the IPI
Rodriguez 2005[93] (abstract only)	Phase II USA Follow-up 3 years	Mixed First-line Aged >60 years (>60=53%)	CHOP with rituximab (no rituximab for T-cell histology) (n=73)	Median age: 61 years (22-80)	NR	This regimen, with sphingosomal vincristine in CHOP +/– rituximab, has a high ORR. It is a well-tolerated therapy with mild neurotoxicity for all patients. At 3 years, the PFS in elderly patients with DLCL treated with R-CHOP is comparable to that of younger patients, despite a larger fraction of high risk IPI in the older patients. This regimen merits randomised comparison to R-CHOP in DLCL
Hainsworth 2003[94]	Phase II Multicentre Follow-up 48	DLBCL First-line/maintenance	R-CNOP (73%) or R-CVP (27%) plus maintenance	Median age: 78 years (61-90) Male: 29%	To evaluate a novel regimen for the first-line treatment of patients with	This abbreviated course of rituximab/chemotherapy, followed by maintenance

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
	months 2003-2007	Aged ≥60 (>80=43%) Ann Arbor stage: II=20%; III=47%; IV=33%	(n=51)	ECOG PS: 0=20%; 1=43%; 2=37% IPI: L=8%; LI=20%; HI=37%; H=35%	DLBCL who were not considered candidates for full-course R-CHOP chemotherapy	rituximab, was active and well tolerated in these very elderly patients. Brief-duration rituximab/chemotherapy as well as maintenance rituximab merit further evaluation in this setting
Cervetii 2003[95]	Single centre Italy 1999-2002	DLBCL II=49% III=23% IV=29% Mixed treatment lines Aged >60	P-VBECDNX (n=35) (26 evaluable for response)	Median age: 69.2 years (60-85) Male: 60% IPI: 0-1=74% 2-3=26%	To evaluate the activity and toxicity of DaunoXome substituted for Doxorubicin in P-VABEC regimen in elderly NHL patients	PVABEC-like regimens are able to induce a high ORR in a percentage of patients affected by aggressive lymphoma and shows that DaunoXome is as effective as Daunorubicin in these disorders, but its acute toxicity is reduced
Gregory 2003[96]	Phase II Multicentre US 20.6 months (1-50) Funding: Amgen,	Aggressive First-line Aged ≥60=44%	CHOP-14 plus G-CSF (n=120)	Median age: 54.5 years (18-84) Male: 52% KPS: <60=1%; 60-80=24%; 90-100=75% IPI: L=34%; LI=32%; HI=27%; H=7%	To evaluate the safety and efficacy of CHOP-14 plus G-CSF in elderly patients with aggressive NHL	Standard-dose CHOP administered every 14 days with prophylactic G-CSF support was delivered as planned in most patients and produced response rates comparable to those with CHOP given every 3 weeks, without exceptional toxicity
Bernardi 2003[97] (abstract only)	Multicentre Italy Follow-up 12 months (1-27) 2000-2002	Aggressive Stage: I-II=63% III-IV=36% Aged >70	CHOP or CEOP or CVP (n=23)	Median age: 74 years (70-89)	NR	We strongly believe that this approach based on CGA is suitable and highly effective for all non-fragile elderly patients affected by aggressive NHL
Tsavaris 2002[98]	Phase II Multicentre Greece	Aggressive Stage III-IV Aged >70	CHOP with pegylated liposomal doxorubicin (n=25)	Median age: 79 (75-82) Male: 64% Median KPS: 90 (70-100) IPI: LI=48%; HI=40%; H=12%		Pegylated liposomal doxorubicin is an effective and well-tolerated component that may be substituted for doxorubicin in the CHOP regimen for the treatment of aggressive NHL in elderly people

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
Angrilli 2002[99] (abstract only)	Phase II Single centre Italy Follow-up 72 months (7-77) 1996-2001	Intermediate/high grade (aggressive) Stage: II=16%, IIE=27%, III-IV=57% Aged >70	D-VICEMB (n=30)	Median age: 74 years (70-85) Male: 47% PS: <80%=63% >80%=37% Karnofsky: <60=37% aaIPI: 0-1=33% 2-3=67%	NR	The protocol is well tolerated and effective in treating very elderly patients with aggressive NHL, as the patients in CR had a sustained DFS. The lack of difference between two age-subgroups suggests that age in itself is not a poor prognostic factor
Martino 2002[100]	Phase II Multicentre Spain Follow-up 13 (1-32) 1998-2000 Funding: Schering-Plough	DLBCL Ann Arbor Stage II=39% III=18% IV=42% First-line Aged >60 (≥70=78.8%)	CCOP (n=33)	Median age: 74 (61-83) Male: 39.4 ECOG PS: 0-1=58% ≥2=42% IPI: L-LI=51% HI-H=49%	To analyse the feasibility of CCOP in patients aged >60	These results suggest that CCOP appears to be an acceptable alternative for elderly patients with DLBCL, and randomised trials against a conventional doxorubicin-containing regimen are justified
Zinzani 2001[101]	Phase II Single centre Italy 1998-2000	Aggressive: DLBCL=75%; PTCL=15%; ALTCL=10% Relapsed Aged ≥60 Stage: II=25%; III=45%; IV=30%	NAEPP plus G-CSF (n=20)	Median age: 73 years (65-80) Male: 60%	To assess the efficacy and toxic profile of the NAEPP protocol in a particularly troublesome subset of patients: pre-treated elderly patients with aggressive NHL	These preliminary data suggest that the NAEPP regimen is an effective combination with a low toxicity profile in elderly pre-treated patients with aggressive NHL. Further trials using NAEPP as a consolidation phase following first-line treatment are needed
Lichtman 2001[102]	US	Aggressive Stage II(bulky)/III/IV Aged ≥65	TNOP (n=26)	Median age: 75.5 years (66-87) Male: 31% PS: 0=12% 1=58% 2=30%	To evaluate toxicity, response rates and survival	We believe that TNOP is an excellent therapeutic option in this group of elderly patients, particularly in the palliative setting

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
NHL – Indolent						
Raty 2012[103]	Phase II Multicentre Finland Follow-up 40 months 2004-2010 Funding: Blood Disease Foundation, Finland	MCL Stage: II A=3% III A=5% IV A=65% IV B=27% First-line Aged >65	Alternating R-CHOP with R-AraC (n=60)	Median age: 74 (65-83) Male: 62 WHO PS: 0=30% 1=47% 2=15% 3=8% IPI: LI=32% HI=40% H=28% MIPI: I-H=98% (I=45%, H=53%)	To investigate whether the poor outcome could be improved, with acceptable toxicity, by prolonging chemoimmunotherapy, up to 10 cycles, combined with rituximab maintenance	Elderly patients with MCL can be treated relatively intensively with acceptable toxicity
Houot 2012[104]	Phase II Multicentre France Follow-up 27 months 2007-2009	MCL Ann Arbor: III=8% IV=92% First-line Aged ≥60	RiPAD+C (n=39)	Median age: 72 (60-80) Male: 77 PS: 0-1=87% 2=13%	To evaluate feasibility and efficacy of RiPAD-C as a treatment for elderly patients with MCL	The bortezomib-containing RiPAD+C regimen results in high CR rates and prolonged PFS with predictable and manageable toxic effects in elderly patients with MCL
Jerkeman 2011[105] (abstract only)	Phase I Denmark and Sweden	MCL II-IV First-line Aged >65	LEN plus R-B (n=12)	Median age: 72.5 (66-85) IPI=MIPI (MCL IPI) I=33.3% H=66.6%	NR	The addition of LEN to the R-B regimen leads to increased toxicity in elderly patients with MCL. Early data indicate a high response rate
Magni 2011[106] (abstract only)	Multicentre Italy 2011	MCL Stage IV=95% First-line Aged ≥60	Ofatumumab, bendamustine and dexamethasone (n=19)	Median age: 69 years (60-81) Male: 79 IPI=MIPI: L=42% I=42% H=16%	NR	Chemotherapy with bendamustine and ofatumumab appears generally safe and well tolerated to date in MCL patients aged 65 years requiring treatment. Preliminary data about efficacy are encouraging: accrual is ongoing for further evaluation
Ruan 2010[107]	Phase II USA	MCL III-IV=96%	RT-PEPC (n=25)	Median age: 68 (52-81) Male: 76	To assess the safety and efficacy of RT-PEPC	RT-PEPC had significant and durable activity in MCL with

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
	Follow-up 38 months Funding: American Society of Clinical Oncology (ASCO) Young Investigator Award, ASCO Career Development Award	Second-line [median previous therapies=2 (1-7)] Aged ≥50	(22 evaluable)	PS by group IPI: LI=28% HI=52% H=20% MIPI: L=8% I=12% H=80%		manageable toxicity and maintained QoL. Novel, low-intensity approaches warrant further evaluation, potentially as initial therapy in elderly patients
Visani 2008[108]	Italy 24 months (18-27) 2005-2006 Supported in part by AIL Pesaro Onlus.	Aggressive B Cell (DLBCL or FL) II=25% III=10 % IV=65% Aged >60	R-COMP-21 (n=20)	Median age: 73 years (61-82) Male: 65% WHO PS: 0-1=55% 2-3=45% IPI: L=10% LI=15% HI=30% H=45%	To evaluate the efficacy and toxicity of R-COMP-21 in the treatment of frail elderly patients	R-COMP-21 is an effective regimen with promising response rates for frail and elderly patients with aggressive NHL
Case Jr 2007[109]	Phase II Multicentre US 18.7 months (13.1-21.4) 2000-2002 Funding: Amgen Inc	Aggressive B-cell Aged >60 (>60=59%) Stage: >60: IA=0%; II=8.3%; III=36.7%; IV=55.0% ≤60: IA=2.4%; II=24.4%; II=43.9%; V=29.3%	R-CHOP plus G-CSF (n=101)	Median age: 72 years (60-88) Male: 50% KPS: 90-100=60.0%; 70-80=33.3%; 60=6.7% IPI: L=6.7%; LI=26.7%; HI=32.0%; H=31.6%	To determine response, toxicity and DFS	Patients aged >60 years receiving R-CHOP with filgrastim support in all cycles received comparable doses of chemotherapy and had similar objective response rates compared with those of younger patients receiving no pre-emptive cycle-1 filgrastim
Fabbri 2007[110]	Phase II Italy Follow-up 37 months 2004-2006	Indolent; SLL=32% MZL=52% FL=16% Stage: II=4% III=16% IV=80% First-line	Low-dose fludarabine plus cyclophosphamide (n=25)	Median age: 74 (66-85) Male: 44% PS: 0=4% 1=52% 2=44% IPI: L-LI=40% HI-H=60%	NR	In conclusion, we believe that rituximab in combination with our regimen may favourably increase results, particularly by prolonging the EFS. This has prompted us to start a new trial including this drug

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
		Aged >65				
NHL – Mixed or undefined						
Gimeno 2011[111]	Single centre Spain Follow-up 24 months 2002-2008	DLBCL=65.7% FL=14.3% B-cell=8.6% T-cell=8.6% Ann Arbor I=11.4% II=28.6% III=11.4% IV=48.6% First-line Aged ≥60	R-CMyOP (n=35)	Median age: 76 (61-88) Male: 57.1 ECOG PS: 0-1=51.4% 2-3=48.6% IPI: L=20% LI=28.6% HI=14.3% H=37.1%	In this study, we have prospectively evaluated the toxicity and efficacy of intermediate doses of NPLD in the modified-CHOP regimen with or without rituximab in frail elderly patients with clinically aggressive NHL not eligible for standard anthracycline	In conclusion, our results indicate that modified-CHOP with intermediate doses of NPLD is a safe regimen for frail elderly patients with a high complete remission rate although it has to be used with caution in this population due to the high risk of febrile neutropenia
Mizoroki 2006[112]	Phase II Multicentre Japan Follow-up 60 months 1992-1995 Funding: Grants-in-Aid for Cancer; Ministry of Health, Labor and Welfare	First-line T cell=16%; B Cell=76% Aged ≥70 Stage: I=4%; II=38%; III=29%; IV=29%	LSG12 (VEPA alternating with FEPP (n=45)	Median age: 72 (70-74) Male: 51% PS: 0=38%; 1=38%; 2=24% aaIPI: L=24%; LI=29%; HI=33%; H=11%; NR=2%	NR	Although the outcomes of LSG12 met our expectations with a reduction in severe infection and equivalent CR and OS outcomes compared with LSG4 and CHOP the possibility of a regimen more beneficial than LSG12 for aggressive lymphoma in the elderly patient should be explored because of frequent haematological toxicity and poor compliance in LSG12
Bocchia 2003[113]	Single centre Italy 1996-2000 Funding: MURST	MCL=40%; FL=30%; LL=15%; MZL=15% First-line: 50% Aged >65 Stage IV	Mini-FLEC (n=20)	Median age: (66-82) Male: 55%	To evaluate the efficacy and toxicity of mini-FLEC	We showed the feasibility of mini-FLEC treatment which, with the caution due to the relatively small number of patients, seems to be effective and safe for elderly patients with advanced LG-NHL requiring treatment
Wilson 2002[114]	Phase II Multicentre US 1993-1995	DLBCL, primary mediastinal large B-cell and folicular large B-cell lymphoma First-line	EPOCH (n=50)	Median age: 46 years (20-88) Male: 50% ECOG PS: 0-1=90%; ≥2=10% IPI:	NR	Dose-adjusted EPOCH may represent an improved method of treating large B-cell lymphomas

Study	Details	Population summary	Intervention	Baseline	Study aim	Conclusions
		>60=24% Stage: I-II=26%; III-IV=74%		L=38%; LI=18%; HI=32%; H=12% aaIPI: L=8%; LI=40%; HI=42%; H=10%		
Doorduijn 2000[115]	Single centre The Netherlands Follow-up 14 months 1994-1998	Various types Relapsed or refractory >60=26.7%	EMP (n=79)	Median age: 69 (61-77); 50 (24-60) WHO PS: ≤60: 0-1=69%; 2=22%; 3=7%; 4=2% >60: 0-1=76%; 2=10%; 3=14%; 4=0 IPI: L=44%; LI=28%; HI=14%; H=10%	To evaluate the efficacy and toxicity of EMP	EMP is a new salvage regimen with a relatively low toxicity. It should be considered for patients with relapsed or refractory NHL who are not candidates for standard re-induction therapy and stem cell transplantation

AILT=angioimmunoblastic T-cell lymphoma; ALTCL=anaplastic large T-cell lymphoma; BCL=B-cell lymphoma; DLBLC=diffuse large B-cell lymphoma; DLBCL=diffuse large cell lymphoma; FL=follicular lymphoma; LG-NHL=low-grade NHL; MCL=mantle cell lymphoma; MLBCL=mediastinal large B-cell lymphoma; MZL=marginal zone lymphoma; NHL=non-Hodgkin's lymphoma; PCNSL=primary central nervous system lymphoma; PTCL(-U)=peripheral T-cell lymphoma (unspecified); SLL=small lymphocytic lymphoma;
CGA=comprehensive geriatric assessment; ECOG=Eastern Cooperative Oncology Group; FLIPI=follicular lymphoma International Prognostic Index; (aa)IPI=(age-adjusted) International Prognostic Index; L=low risk; LI=low-to-intermediate risk; HI=high-to-intermediate risk; I=intermediate risk; KPS=Karnofsky Performance Status; MIPI=Mantle Cell international Prognostic Index; PS=performance status; QoL=quality of life; WHO=World Health Organisation; (aa)CCI=(age-adjusted) Charlson comorbidity index; CR=complete response; DFS=disease-free survival; EFS=event-free survival; ITT=intention to treat; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; RR=response rate; TTF=time to treatment failure;
CCNU=1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine); CCOP=pegylated liposomal doxorubicin, vincristine, cyclophosphamide and prednisone; CEMP=cisplatinum, etoposide, mitoxantrone, prednisone; CEOP=cyclophosphamide, vincristine, epirubicin and prednisone; CHO=cyclophosphamide, doxorubicin, and vincristine; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; CHP=cyclophosphamide,
doxorubicin, and prednisone; CMD=irinotecan, mitoxantrone and dexamethasone; COP-X=liposomal daunorubicin, cyclophosphamide, vincristine and prednisone plus G-CSF; CyclOBEAP=doxorubicin, cyclophospamide or etoposide, vincristine, prednisone, with or without bleomycin; DA-POCH-R=dose-adjusted infusional cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy with rituximab; DRCOP=R-CHOP with pegylated liposomal doxorubicin; D-VICEMB=cyclophosphamide, mitoxantrone, etoposide, bleomycin, vinblastine and dexamethasone; EMP=etoposide, mitoxantrone and prednisone; EPOCH=eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone; FEPP=vindesine, etoposide, procarbazine, prednisone; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor; LEN plus R-B=lenalidomide, bedamustine and rituximab; Mini-FLEC=epirubicin, fludaribine, cyclophosphamide; NAEPP=vinorelbine, epirubicin, prednisone; NPLD=non-pegylated liposomal doxorubicin; P-VBECDNX=etoposide, cyclophosphamide, DaunoXome, vincristine, bleomycin, prednisone; R-AraC=cytarabine plus rituximab; R-BM=rituximab, mitoxantrone and bendamustine; R-CCOP=modified R-CHOP (pegylated liposomal doxorubicin, vincristine, cyclophosphamide and prednisone); R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CMD=rituximab, irinotecan, mitoxantrone and dexamethasone; R-CMyOP=NPLD, cyclophosphamide, vincristine and prednisone; R-CNOP=cyclophosphamide, mitoxantrone, vincristine and prednisone plus rituximab; R-CVEP=rituximab, cyclophosphamide, etoposide, prednisone, procarbazine, vorinostat; R-CVP=cyclophosphamide, vincristine and prednisone plus rituximab; R-COMP=cycolphosphamide, vincristine and prednisone plus rituximab; R-GemOx=gemcitabine and oxaliplatin plus rituximab; RiPAD+C=rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil; R-mini-CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab; R-THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone plus rituximab; R-VNCOP-B=etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, and bleomycin, AND RITUXIMAB; RT-PEPC=prednisone, etoposide, procarbazine and cyclophosphamide plus rituximab and thalidomide; THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine and prednisolone; TNOP=thiotepa, novantrone [mitoxantrone], vincristine and prednisone; VEPA=vincristine, cyclophosphamide, doxorubicin, prednisone; NR=not reported

9.2 Efficacy evidence

The majority of studies presented at least one efficacy outcome of interest in relation to time to event outcomes, survival and ORR. Details are presented in Table 15. As discussed in other sections of the report, the outcomes reported by the single cohort studies varied greatly.

9.2.1 Aggressive disease

Time-to-event outcomes

All but one[90] of the included studies that focussed on aggressive disease reported at least one outcome of interest. There were a range of PFS-related outcomes reported across the studies: median PFS, 2-year PFS, 3-year PFS, 3.5-year, 4-year PFS, and 5-year PFS. Six studies[59,63,64,76,77,81] presented data for median PFS, which ranged from 5.9 months[76] at the lower end of the scale to 45 months.[81] Six studies[64,69,75,81,88,94,107] reported 2-year PFS, with results that varied from 24%[107] to 71%;[69,94] one study[75] reported a significant result for fit versus unfit patients (73.4% vs 21.7; p<0.0001). Seven studies[65,68-71,82,93] reported 3-year PFS, which ranged from 17.5%[82] to 82.6%;[68] one study presented results for <60 years versus >60 years, which yielded similar results for both age groups (84% vs 83%).[93] Fina et al[83] reported 3.5-year PFS at 87.5%, and Hainsworth et al[69,94] reported 4-year PFS at 56%. Five-year PFS was reported at 51.8% in Niitsu et al.[87]

Results relating to EFS were reported as median, 1-year, 2-year, 3-year, and 5-year EFS. Zwick et al[78] reported a median EFS of 2.7 months for all patients. For 1-, 2-, and 5-year EFS the results were 45%,[100] 65.5%,[85] and 52%,[58] respectively. The 3-year EFS rates were 71.9%[53] and 54%.[61] Four studies reported DFS: median DFS was reported at 72%;[66] 1-year DFS was 34.8%;[62] 2-year DFS at 57%;[64] and 5-year DFS was reported as 80%.[58] Three studies presented data for median, 2-year, 4-year, and 5-year TTP. Tsurumi et al[81] reported 58 months, 60.4%, and 45.2% for median, 2- and 5-year TTP, respectively, and Tsavaris et al[98] reported a median TTP of 26 months. Corazzelli et al[66] reported a 4-year TTP rate of 77%. Two studies reported FFS: 2-year FFS was 71%,[95] and 3-year FFS was 39%.[71]

Survival outcomes

Survival outcomes were presented in several ways – median, 1-year, 18-month, 2-year, 3.5-year, 4-year, 5-year, and 6-year OS. Ten studies[55,63,64,75-78,81,91,98,102] reported median OS, with the majority[55,63,75-78,91] of studies reporting a median OS of <20 months; three studies reported longer median OS with 29,[64] 32[98] and 51 months.[81] Two-year OS was reported by nine studies,[64,69,72,74,81,85,88,94,95] which varied from 37%[72] to 75%.[74,95] Three-year OS was reported by nine studies,[53,61,65,67-69,71,78,82] all of which reported rates of >50%, apart from Niitsu et al[82] (28.2%). Five-year OS was reported by four studies:[58,77,81,87] two studies[77,81] reported rates <40%, and two studies reported rates >50%.[58,87]

Objective response rates

Thirty-five studies[53,54,57,58,61-68,70,71,73-76,78,82-86,88,89,93,95-97,100-102] reported results for ORR. The majority of studies achieved an ORR of >70%, with two studies achieving 100%.[68,86] One study achieved a much lower result than the others, with an ORR of 33.5%.[101]

9.2.2 Indolent disease

Time-to-event outcomes

Five studies presented time-to-event outcomes. In terms of PFS-related outcomes, median PFS was 26 months in one study;[104] 2-year PFS was reported by two studies[107,109] with similar results for older versus younger patients (75% vs 78%[109]) and a 2-year PFS of 24% for older patients[107]; and 4-year PFS was reported at 70% in another study.[103] Two studies reported EFS outcomes: median EFS was reported at 20 months[110] and 4-year EFS was reported at 66%.[103] Two studies reported DFS. A comparison of mean DFS between older and younger patients showed no statistically significant difference (p=0.44),[109] and 4-year DFS was reported at 77% in another study.[103]

Survival outcomes

Survival was not well reported. Ruan et al reported a 2-year OS of 45%[107], the 3.1-year OS was 70% in Fabbri et al,[110] and 4-year OS was 72% in Raty et al.[103] Houot et al[104] reported that OS was not reached.

Objective response rates

The ORRs were well reported for patients with indolent disease. All studies achieved >70%, with four studies[103,105,106,109] achieving >90%. When age was compared, younger patients responded better than older patients (95% vs 87%; p=0.19).[109]

9.2.3 Mixed or undefined disease

Time-to-event outcomes

Progression-free survival was 33 months in Bocchia et al,[113] and TTP was 8 months in Gimeno et al.[111] The 1-year PFS was 68%[111] and 54%,[115] compared with 58%[111] and 35%[115] for 2-year PFS. The 4-year PFS was 45% in Bocchia et al.[113] A comparison of 5-year PFS between older and younger patients showed no statistically significant difference (24% vs 68%; p=0.85).[114]

Survival outcomes

Median OS was reported by two studies: 51.6 months (4.3 years) in Mizoroki et al[112] and 40 months in Bocchia et al.[113] Rates for 1- and 2-year OS were comparable for two studies that reported these outcomes: 74% and 70% in Gimeno et al,[111] and 41% and 31% in Doorduijn et al.[115] A comparison of 5-year OS between older and younger patients showed no statistically significant difference (58% vs 78%; p=0.14).[114]

Objective response rates

Three studies reported ORR: two studies achieved a high rate of 86%[111] and 85%,[113] and one study achieved a lower rate of 38%.[115]

Table 15 Efficacy outcomes, single cohorts

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
NHL – Aggressive disease				
Shin 2012[53]	Reduced-dose R-CHOP	3-year EFS=71.9%±5.1%	3-year OS=83.3%±5.1%	89.5%
Boccomini 2012[54] (abstract only)	R-BM	NR	NR	96%
Chaibi 2012[55] (abstract only)	R-mini-CHOP	NR	Median survival=11 months	NR
Chiappella 2012[56] (abstract only)	Lenalidomide (15 mg) + R-CHOP-21	75% (57 to 86)	94% (82 to 98)	NR
Fan 2012[57] (abstract only)	R-GemOx	Not achieved	Not achieved	75%
Spina 2012[58]	R-CHOP All patients	5-year DFS=80% (69 to 88) 5-year EFS=52% (42 to 61)	5-year OS=60% (50 to 69) 5-year CSS=74% (63 to 81)	87% (80 to 94)
	Fit	NR	5-year OS=76%	
	Unfit	NR	5-year OS=53%	
	Frail	NR	5-year OS=29% p=0.001	NR
	>80	5-year DFS=67% 5-year EFS=46%	5-year OS=54% 5-year CSS=68%	
	70-80	5-yeat DFS=84% 5-year EFS=67% DFS: p=0.11 EFS: p=0.06	5-year OS=61% 5-year CSS=75% OS: p=0.24 CSS: p=0.91	
Straus 2012[59] (abstract only)	R-CVEP	PFS=10 months	NR	NR
Rodriguez 2011[60] (abstract only)	DRCOP	78%	77%	NR
Musolino 2011[61]	DA-POCH-R ITT (23 patients)	NR	3-year OS=56% (40 to 80)	83% (68 to 98)

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
	Evaluable (21 patients)	3-year EFS=54%	3-year OS=54%	90% (77 to 100)
	≤80	EFS was worse in >80, p=0.006	NR	92% (77 to 100)
	>80		NR	89% (69 to 100)
Zinzani 2011[62]	Lenalidomide plus rituximab	1-year DFS=34.8% (14.4 to 56.2)	18-month OS=55.1% (32.3 to 72.9)	After induction phase=35%
Weidmann 2011[63]	Bendamustine plus rituximab	PFS=7.7 months	7.7 months	69 (44 to 94)
Peyrade 2011[64]	R-mini-CHOP	PFS=21 months (13 to not reached) 2-year PFS=47% (38 to 56) 2-year DFS=57% (42 to 68)	OS=29 months (21 to not reached) 2-year OS=59% (49 to 67)	73%
Kasahara 2011[65]	R-THP-COP All patients	3-year PFS=53%	3-year OS=63%	96%
	<76	3-year PFS=46%	3-year OS=59%	94%
	≥76	3-year PFS=65%	3-year OS=71%	100%
Corazzelli 2011[66] (abstract only)	R-COMP-14	4 year TTP 77% (64 to 91) DFS 72% (55 to 90)	4-year OS 67% (52 to 83)	73%
Boggiani 2010[67] (abstract only)	DA-R-CHOP	EFS=54%	3 year 56%	90%
Ishii 2010[68]	R-VNCOP-B All patients	3-year PFS=82.6%	3-year OS=76.4% 3-year OS=100% 3-year OS=67.5%	100%
	IPI L	3-year PFS=100%		
	IPI H	3-year PFS=66.7%		
Hainsworth 2010[69]	Brief duration R-CNOP or R-CVP All patients	2-year PFS=71% 3-year PFS=65% 4-year PFS=56%	2-year OS=72% 3-year OS=67% 4-year OS=67%	NR
	≥80	p=0.0251	p=0.3363	
	<80			

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
Chang 2010[70]	R-CHOP plus GM-CSF	3-year PFS=78% (60 to 88) EFS=47% (31-62)	84% (68% to 93%)	92%
Luminari 2010[71]	R-COMP	3-year PFS=69% (56 to 79) 3-year FFS=39% (28 to 51)	3-year OS=72% (58 to 82)	71%
Noga 2010[72] (abstract only)	R-CHOP	NR	1-year survival=65% 2-year survival=37% [Excluding patients who discontinued in/or after cycle 1; 1-year=73% 2-year=42% Excluding non-lymphoma related deaths; 1-year=85% 2-year=71%]	NR
Vacirca 2010[73] (abstract only)	Bendamustine plus rituximab	NR	NR	51.6%
Fauveau 2009[74] (abstract only)	Idarubicin	NR	2-year survival All=75% Dose level 2=58%	79%
Tucci 2009[75]	CHOP/CHOP-like therapy (74%) or palliative therapy CGA=Fit	2-year PFS=73.4%	Median OS=not reached 2-year OS=77.6%	92.8%
	CGA=Unfit	2-year PFS=21.7% p<0.0001	Median OS=8 months 2-year OS=23.8% p<0.0001	52.3% p< 0.0001
	Chemotherapy	2-year PFS=55.9%	Median OS=8 months 2-year OS=57.7%	79.9%
	Palliative therapy	2-year PFS=22.2% p=0.0002	Median OS=7 months 2-year OS=26.1% p=0.0003	50%
	Unfit with chemotherapy	NR	2-year OS=19.8%	NR

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
	Unfit with palliative therapy	NR	2-year OS=26.1% p=0.85	NR
Illerhaus 2009[76]	Methotrexate, rocarbazine + CCNU	5.9 (2.7 to 26.6)	15.4 (7.6 to 65.1)	70.4%
Mitchell 2008[77]	COP-X	PFS=13.4 months	OS=18.6 months 5-year survival=35% NHL-specific survival=37%	NR
Zwick 2008[78]	CEMP – bolus vs continuous infusion etoposide All patients	Median EFS=2.7 months	Median OS=10 months (1-127)	34%
	Primary refractory	EFS=2 months	6 months 1-year OS=20% 2-year OS=10% 3-year OS=5%	
	Relapse after <1 year	EFS=4 months	11 months 1-year OS=27% 2-year OS=18% 3-year OS=18%	
	Relapse after ≥1 year	EFS=7 months	17 months 1-year OS=75% 2-year OS=38% 3-year OS=31%	
Isidori 2007[79] (abstract only)	R-COMP-21	NR	90% (at 14 month follow-up)	NR
Tsurumi 2007[81]	THP-COP All patients	PFS=41 months 2-year PFS=42.6% 5-year PFS=30.5% TTP=58 (1 to 106) 2-year TTP=60.4% 5-year TTP=45.2%	2-year OS=47.9% 5-year OS=38.1%	NR
	70-79	PFS=45 months	OS=51 months	

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
		2-year PFS=48.9% 5-year PFS=32.4% TTP=62 (1 to 106) 2-year TTP=64.7% 5-year TTP=45.4%	2-year OS=52.9% 5-year OS=40.3%	
	≥80	PFS=24 months 2-year PFS=32.1% 5-year PFS=18.2% TTP=39 (1 to 74) 2-year TTP=48.2% 5-year TTP=36.2%	OS=31 months 2-year OS=32.1% 5-year OS=24.6%	
	IPI L-LI	NR	2-year OS=85.7% 5-year OS=77.9%	
	IPI IH-H	NR	2-year OS=26.7% 5-year OS=15.6% p<0.01	
Niitsu 2007[82]	CMD All patients	3-year PFS=17.5%	3-year survival=28.2%	60%
	Relapsed patients	3-year PFS=20.8%	3-year survival=35.8%	74%
	Refractory patients	3-year PFS=0	3-year survival=10.2%	40%
Fina 2007[83]	R-VNCOP-B	3.5-year PFS=87.5%	3.5-year OS=91.5%	96%
Wolf 2006[84]	CHOP-14 with pegfilgrastim	NR	NR	76%
Zaja 2006[85]	Modified R-CHOP (R-CCOP)	2-year EFS=65.5%	2-year OS=68.5%	76%
Rigacci 2006[86]	R-CHOP-14 with G-CSF All patients	DFS=70% (after a median of 17 months	OS=79% (after median of 23 months)	100%
Niitsu 2006[87]	CyclOBEAP All patients	5-year PFS=51.8% (46-57) 60.3% (60-69)	5-year OS=60.6% (57-65)	NR

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
	DLBCL	56%	64.9% (64-74)	
	IPI LI	54%	70% (63-73)	
	IPI IH	42%	56% (53-61)	
	IPI H		62.5% (56-67)	
Niitsu 2006[88]	R-CMD	2-year PFS=37.2%	2-year survival=45.2%	74%
Desch 2005[89] (abstract only)	R-CHOP <60	NR	NR	97%
	>60	NR	NR	91%
Federico 2005[90] (abstract only)	R-COMP	NR	NR	NR
Monfardini 2005[91]	Vinorelbine and prednisone	NR	OS=10 months	NR
Goto 2005[92]	CHOP or THP/COP <60	DFS 58%	p<0.05	NR
Rodriguez 2005[93] (abstract only)	R-CHOP >60 years	3-year PFS=83% all patients (66 to 92) 3-year PFS=86% DLCL patients only (66 to 94)	NR	91.9%
	≤60 years	3-year PFS=84% all patients (66 to 93) 3-year PFS=85% DLCL patients only (66 to 94)	NR	93.5%
Hainsworth 2003[94]	R-CNOP/R-CVP	2-year PFS=71% 3-year PFS=65% 4-year PFS=56%	2 year=72% 3 year=67% 4 year=67%	NR
Cervetti 2003[95]	P-VBECDNX	2-year FFS=71%	2 year 75%	77%

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
Gregory 2003[96]	CHOP-14 plus G-CSF All patients	At a median of 20.6 months DFS=52%	At a median of 20.6 months survival=77%	89%
	≥60	At a median of 22.3 months DFS=53%	At a median of 22.3 months survival=74%	85%
	<60	NR	NR	93%
Bernardi 2003[97] (abstract only)	CHOP/CEOP/CVP	NR	NR	90%
Tsavaris 2002[98]	CHOP (CCOP)	TTP=26 months (14->42)	OS=32 months (26-48)	NR
Angrilli 2002[99] (abstract only)	D-VICEMB	50% DFS 63% (of those in complete remission)	(at 72 months) 50% PS >80%=71% <80%=30% aaIPI 0-1=71% 2-3=18% (p<0.02) Age <75=51% >75=47%	NR
Martino 2002[100]	CCOP	1-year EFS=45% (28-62) Among patients with objective response=64% (43-85)	1-year OS=55% (38-72)	64%
Zinzani 2001[101]	NAEPP All patients	NR	NR	65%
	DLBCL			67%
	PTCL			33.5%
	ALCL			100%
Lichtman 2001[102]	TNOP	NR	26 months 1-year survival=81% 2-year survival=54%	57%
NHL – Indolent				
Raty 2012[103]	Alternating R-CHOP/R-AraC	4-year PFS=70% 4-year EFS=66% 4-year DFS=77% (patients with	4-year OS=72%	95%

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
		CR/CRu)		
Houot 2012[104]	RiPAD+C Overall	PFS=26 months	OS=Not reached	NR
	After 4 cycles	NR	NR	79%
	After 6 cycles	NR	NR	74% - ITT analysis (all patients)
Jerkeman 2011[105] (abstract only)	LEN plus R-B	NR	NR	100% (out of 10 patients)
Magni 2011[106] (abstract only)	Ofatumumab, bendamustine and dexamethasone	NR	NR	94%
Ruan 2010[107]	RT-PEPC	PFS/TTP=10 months (5-23) 2-year PFS=24 (10-56)	2-year OS=45% (28-76)	73% (50-89)
Case Jr 2007[109]	R-CHOP + G-CSF >60	2-year PFS=75%	NR	87%
	≤60	2-year PFS=78% DFS >60 vs ≤60, p=0.44		95% p=0.19
	IPI low risk	Mean DFS=22.4 months	NR	NR
	IPI high risk	Mean DFS=14.1 months		
Fabbri 2007[110]	Low-dose fludarabine plus cyclophosphamide All patients	EFS=20 months	3.1-year OS=70%	84%
	SLL	NR	NR	87.5%
	MZL			77%
	FL			100%
NHL – Mixed or undefined				
Mizoroki 2006[112]	VEPA/FEPP	NR	4.3 years (1.9-5.9) 4 year=50%	NR
Gimeno 2011[111]	R-CMyOP	TTP=8 (1-28) 1-year PFS=68% (52-83)	1-year OS=74% (60-87) 2-year OS=70% (54-85)	86%

Study	Intervention	Median PFS/TTP (95% CI) Months	Median OS (95% CI) Months	ORR % (95% CI)
		2-year PFS=58% (40-76)		
Bocchia 2003[113]	Mini-FLEC	PFS=33 months (6-58) 4-year PFS=45%	OS=40 months (4-61) 4-year OS=48%	85% (previously untreated patients=100%)
Wilson 2002[114]	EPOCH ≤60	62-month PFS=68%	62-month OS=78%	NR
	>60	62-month PFS=24% p=0.85	62-month OS=58% p=0.14	NR
Doorduijn 2000[115]	EMP All patients	1-year PFS=54% 2-year PFS=35% -text, (30% - abstract)	1-year OS=41% 2-year OS=31%	38%
	>60	NR	2-year OS=49%	67%
	Prior CR		Median survival=17 months	NR
	No prior CR		Median survival=5 months p=0.07	

DLBLC=diffuse large B-cell lymphoma; DLCL=diffuse large cell lymphoma; FL=follicular lymphoma; MZL=marginal zone lymphoma; NHL=non-Hodgkin's lymphoma; PTCL=peripheral T-cell lymphoma; SLL=small lymphocytic lymphoma;

CGA=comprehensive geriatric assessment; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; (aa)IPI=(age-adjusted) International Prognostic Index (L=low risk; LI=low-to-intermediate risk; HI=high-to-intermediate risk; I=intermediate risk); KPS=Karnofsky Performance Status; PS=performance status; CR=complete response; CSS=cause specific survival; DFS=disease-free survival; EFS=event-free survival; FFS-failure-free survival; ITT=intention to treat; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TTP=time to disease progression;

CCNU=1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine); CCOP=pegylated liposomal doxorubicin, vincristine, cyclophosphamide and prednisone; CEMP=cisplatinum, etoposide, mitoxantrone, prednisone; CEOP=cyclophosphamide, vincristine, epirubicin and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; CMD=irinotecan, mitoxantrone and dexamethasone; COP-X=liposomal daunorubicin, cyclophosphamide, vincristine and prednisone plus G-CSF; CyclOBEAP=doxorubicin, cyclophospamide or etoposide, vincristine, prednisone, with or without bleomycin; DA-POCH-R=dose-adjusted infusional cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy with rituximab; DRCOP=R-CHOP with pegylated liposomal doxorubicin; D-VICEMB=cyclophosphamide, mitoxantrone, etoposide, bleomycin, vinblastine and dexamethasone; EMP=etoposide, mitoxantrone and prednisone; EPOCH=eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone; FEPP=vindesine, etoposide, procarbazine, prednisone; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor; LEN plus R-B=lenalidomide, bedamustine and rituximab; Mini-FLEC=epirubicin, fludaribine, cyclophosphamide; NAEPP=vinorelbine, epirubicin, prednisone; NPLD=non-pegylated liposomal doxorubicin; P-VBECDNX=etoposide, cyclophosphamide, DaunoXome, vincristine, bleomycin, prednisone; R-AraC=cytarabine plus rituximab; R-BM=rituximab, mitoxantrone and bendamustine; R-CCOP=modified R-CHOP (pegylated liposomal doxorubicin, vincristine, cyclophosphamide and prednisone); R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CMD=rituximab, irinotecan, mitoxantrone and dexamethasone; R-CMyOP=NPLD, cyclophosphamide, vincristine and prednisone; R-CNOP=cyclophosphamide, mitoxantrone, vincristine and prednisone plus rituximab; R-CVEP=rituximab, cyclophosphamide, etoposide, prednisone, procarbazine, vorinostat; R-CVP=cyclophosphamide, vincristine and prednisone plus rituximab; R-COMP=cycolphosphamide, vincristine and prednisone plus rituximab; R-GemOx=gemcitabine and oxaliplatin plus rituximab; RiPAD+C=rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil; R-mini-CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab; R-THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone plus rituximab; R-VNCOP-B=etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, and bleomycin, rituximab; RT-PEPC=prednisone, etoposide, procarbazine and cyclophosphamide plus rituximab and thalidomide; THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine and prednisolone; TNOP=thiotepa, novantrone [mitoxantrone], vincristine and prednisone; VEPA=vincristine, cyclophosphamide, doxorubicin, prednisone; NR=not reported

9.3 Tolerability evidence

Outcomes relating to tolerability for the included single cohort studies are presented in Table 16.

9.3.1 Aggressive disease

Few studies reported information relating to RDI or treatment completion. Two studies[79,90] reported an RDI of >80, and five studies[53,65,80,86,89] reported an RDI of >90. A comparison of RDI between older and younger patients in one study[89] showed no statistically significant difference. Gregory et al[96] reported that 86% of all patients completed the planned 6 cycles, and Tsurumi et al[81] reported that 80% of patients aged 70-79 years and 55.6% of patients aged >80 received the planned 6 cycles. In terms of discontinuations, the main reasons given for discontinuing or withdrawing from treatment were toxicity, death, or progressive disease. Eighteen studies[53,56,61,63,65,68,71,74,77,80,86,87,90,91,96,100,102] presented data regarding dose reductions or delays, using percentage of patients or cycles as a common measure.

9.3.2 Indolent disease

Two studies reported RDI: Visani et al[108] reported an RDI of 83%, and Case Jr et al[109] reported 91% and 93% for older and younger patients, respectively. In terms of discontinuations, the main reasons given for discontinuing or withdrawing from treatment were toxicity, death, or progressive disease. Three studies[103,108,109] presented outcomes relating to dose delays or reductions. Adverse events were reported by all studies.[103-110]

9.3.3 Mixed or unclear disease

None of the studies reported data relating to RDI or treatment completion. Three studies[111-113] reported data relating to discontinuations or withdrawals, and two studies[111,113] reported on delays and reductions.

Table 16 Tolerability, single cohorts

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
NHL – Aggressive disease				
Shin 2012[53]	Reduced-dose R-CHOP 6 or 8 cycles Median cycles per patient=6 (range 1-8) RDI: Doxorubicin=97.3% Cyclophophamide=97.4% Vincristine=95%	NR	Dose reduction in 20% of patients in 12.1% of cycles Chemotherapy was delayed in 9.4% of patients in 1.8% of cycles 77.6% of patients completed the planned 6-8 cycles.	Grade 3-4: Neutropenia=35.3% Leukopenia=31.8% Asthenia=13%
Boccomini 2012[54] (abstract only)	NR	R-BM 6% withdrawal – cardiac toxicity 6 patients did not complete treatment, due to; Progressive disease=1 patient AEs=4 patients Worsening PS=1 patient Death=2 patients, due to: Lymphoma after 2nd-line treatment=1 patient Other cancer=1 patient	NR	Neutropenia=18%
Chaibi 2012[55] (abstract only)	NR	NR	NR	R-mini-CHOP Grade 3-4 toxicity; Neutropenia=28% Thrombocytopenia=12%
Chiappella 2012[56] (abstract only)	NR	NR	Lenalidomide (15 mg) + R-CHOP21: 14% dose reductions 5% without lenalidomide (neutropenia) 94% of cycles administered	Thrombocytopenia=13% of cycles Neutropenia=33% of cycles Grade 3 non-haematological toxicity=14% of patients
Fan 2012[57] (abstract only)	NR	NR	NR	R-GemOx Grade 3-4 toxicities; Bone marrow depression=25% Gastrointestinal=16.7%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Spina_2012 [58]	R-CHOP or variants: Median cycles per patient=6 (range 1-7) 23%=R-CHOP; 16%=CHOP; 11%=CEOP; 4%=R-CEOP; 1%=CVP; 8%=75% R-CHOP; 9%=75% R-CEOP; 7%=75% CEOP; 10%=50% R-CVP; 3%=50% CVP	Discontinuation due to: disease progression=9% pulmonary embolism=2% Deaths=5 patients (4 toxic, 1 embolism) Unfit and frail patients had a higher risk for death than fit patients (HR, 1.96 for unfit patients and 2.55 for frail patients; p=0.1)	NR	Grade 4 neutropenia=14% (Grade 3-4=30%) Grade 3-4 mucositis=12% 4 deaths due to toxicity
Straus 2012 [59] (abstract only)	NR	R-CVEP 7.7% withdrew - toxicity	NR	NR
Musolino 2011 [61]	DA-POCH-R 91% completed treatment	NR	Cycles delivered on time=58 Dose increases (≥144% dose)=40% of cycles Dose reduction=43% of patients in 57% of cycles Therapy delays=33% of patients in 12% of cycles	Grade 3-4; Neutropenia=48% Thrombocytopenia=9% Anemia=13% Neutropenic fever=13% Oral mucositis=4%
	NR	NR	NR	≤80 Grade 3-4; Neutropenia=46% Thrombocytopenia=8% Anemia=13% Neutropenic fever=8% Oral mucositis=0
	NR	NR	NR	>80 Grade 3-4; Neutropenia=50% Thrombocytopenia=9% Anemia=10% Neutropenic fever=15% Oral mucositis=10%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Zinzani 2011[62]	NR	NR	NR	Lenalidomide plus rituximab Grade 3-4: Neutropenia=30% Thrombocytopenia=14%
Weidmann 2011[63]	NR	NR	Bendamustine plus rituximab: Delays=57% of patients in 33% of cycles, due to: Patient preference=6 cycles Haemotoxicity=5 cycles Infections=3 cycles Diarrhoea=2 cycles	Grade 3-4; Neutropenia=23% Leukopenia=11% (of cycles) Grade 3 infections=10% (of cycles)
Peyrade 2011[64]	NR	R-mini-CHOP Discontinuation=27.5%	NR	Grade ≥3 neutropenia=40% 12 toxic deaths
Kasahara 2011[65]	R-THP-COP RDI: 95.4% (THP) 95.1% (COP)	Discontinuation=30.8%, due to: Progression=13.5% Independent complication=3.8% Febrile neutropenia=3.8% PS progression=1.9% Personal choice=7.7%	10.6% of cycles delayed, due to: Non-haematological AE=8 cycles Haematological AE=14 cycles Both types of AE=2 cycles Non-treatment related=4 cycles	Grade 3-4; Anaemia=29% Neutropenia=85% Thrombocytopenia=14% Febrile neutropenia=10% Grade 3; Fever/infection=13.5%
Corazzelli 2011[66] (abstract only)	R-COMP-14 67% completed all 6 cycles	6 due to toxicity Deaths=29%, due to; Toxic event=3 patients Progressive disease=6 patients		NR
Ishii 2010[68]	NR	R-VNCOP-B Discontinuation=2 patients (8.7%), due to: Hepatitis C=1 patient PS progression=1 patient	Reduced dose=8.7% of patients	Grade 3-4; Neutropenia=75% Febrile neutropenia=30% Thrombocytopenia=10%
Hainsworth 2010[69]	NR	Brief duration R-CNOP or R-CVP Discontinuation=6%, due to: Progression=2% Gastrointestinal haemorrhage=2% Intercurrent event=2% Discontinuation of maintenance rituximab=2%	NR	Grade 3-4 toxicity; Neutropenia=41% Thrombocytopenia=12%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		Deaths=17 patients (9 patients lymphoma, 3 patients intercurrent illness, 5 patients unknown)		
Chang 2010[70]	R-CHOP 81.1% of planned therapy cycles were administered	8 patients (21%) discontinued the protocol therapy as a result of toxicity related to R-CHOP chemotherapy	NR	Grade 3 Leukopenia=32% Neutropenia=13% Thrombocytopenia=24% Haemoglobin=21% Infection=11% Nausea=11% Neuromotor=11% Neurosensory=16% Grade 4 Leukopenia=29% Neutropenia=42%
Luminari 2010[71]	R-COMP 72% completed 6 cycles 58% completed all 8 cycles	Reasons for discontinuation: AEs=22.2% SD/PD=12.5% Physicians decision=5.6% Patient refusal=1.4%	5% of cycles delayed due to toxicity Treatment delay in 19 patients	Any grade 3-4 AE=88%; Neutropenia=54% Febrile neutropenia=18%
Noga 2010[72] (abstract only)	NR	NR	NR	R-CHOP Grade 3 AEs: Neutropenia=24% Febrile neutropenia=12% Thrombocytopenia=24% Cardiac=12% Grade 4 AEs: Neutropenia=41% Febrile neutropenia=12%
Vacirca 2010[73] (abstract only)	Bendamustine plus rituximab Median cycles per patient=3	NR	NR	Grade 3-4: Neutropenia=30.3% Anaemia=12.1% Thrombocytopenia=12.1%
Fauveau 2009[74] (abstract only)	NR	Idarubicin with oral cyclophosphamide etoposide, prednisolone and intravenous rituximab Discontinuations=2 patients	Dose reduction=8 patients	Grade 3-4 infection occurred in 16% in level 2 and 10% in level 3

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Illerhaus 2009[76]	NR	NR	NR	Methotrexate, rocarbazine + CCNU Grade 3-4 toxicities; Neutropenia=64% Thrombocytopenia=29% Anaemia=32% Grade 3 toxicities; Infection=27%
Mitchell 2008[77]	COP-X Mean cycles per patient=6 (1-8)	Discontinuation=43% of patients, due to: AEs=4 patients Patient request=2 patients Investigators request=4 patients Progression=9 patients	DaunoXome dose reduction in 8.3% of cycles, 20% of patients due to drug-related AEs Treatment delay of 1 cycle in 25.5% of patients (9.8% due to haematoxicty, 15.7% unrelated AEs)	Grade 3-4 toxicity; Abdominal pain=18% Skeletal pain=12% Infection=11.8% Grade 4 toxicity; Neutropenia=71% Thrombocytopenia=14%
Zwick 2008[78]	CEMP=bolus vs infusional etoposide All patients 32% of patients completed all 5 cycles, main reason=insufficient response	3 patients discontinued after 1 and 2 cycles due to toxicity/concomitant disease	NR	NR
	NR	NR	NR	Bolus: Leukocytopenia=83.8% of cycles Thrombocytopenia=31.6% Anaemia=6.3%
	NR	NR	NR	Infusional Leukocytopenia=88.2% of cycles, p=0.737 Thrombocytopenia=44.4%, p=0.42 Anaemia=15%, p=0.092
Isidori 2007[79] (abstract only)	R-COMP-21 RDI=83%	NR	17% dose delay due to haematological toxicity	Any grade 3-4 WHO toxicity=15% Neutropenia=16%
Tsurumi 2007[81]	THP-COP 70-79=80% completed all 6 cycles	NR	NR	70-79 Grade 3-4; Neutropenia=42% Febrile neutropenia=13%
	≥80=55.6% completed all 6 cycles	NR	NR	≥80 Grade 3-4;

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				Neutropenia=38% Febrile neutropenia=13%
Niitsu 2007[82]	NR	NR	NR	CMD Grade 3-4 haematological toxicity=60% Grade 4 neutropenia=27% Grade 3-4 thrombocytopenia=16.7% Grade 3 febrile neutropenia=26.7%
Fina 2007[83]	NR	NR	NR	R-VNCOP-B Grade 3-4 neutropenia=25%
Mey 2007[80]	R-CHOP-14 with pegfilgrastim RDI=93.2% 87.5% of cycles were received on time and at planned dose	NR	Delays=12.5% (9 ocassions), due to: Delayed haematopoietic recovery=1.8% of cycles Non-haematological toxicity=8.3% of cycles Patients request=1.4% of cycles (All delays were in patients >70)	Grade 3 toxicity; Granulocytopenia=20% Thrombocytopenia=10% Nausea=20% Emesis=20% Febrile neutropenia=10% Mucositis=20% Asthenia=10% Alopecia=100% Grade 4 toxicity; Granulocytopenia=80% Thrombocytopenia=10% Diarrhoea=10% Febrile neutropenia=10% [Note; only 10 patients included in study]
Wolf 2006[84]	CHOP-14 with pegfilgrastim Median number of cycles supported by pegfilgrastim=6 (range 1-6) 47% (range 28-66) of patients received full dose on schedule for all cycles Full dose by cycle: 2=79% 3=86% 4=93% 5=65% 6=90%	Withdrawals=5 patients, due to: Neutropenic sepsis=2 patients (after cycles 5 and 6) *Klebsiella pneumonia* sepsis=1 patient (after cycle 5) Administrative reasons=1 patient (after cycle 3)	Delays=10 patients (33.3%) on 15 occasions (largest in cycle 2) due to: Haematological toxicity=9 delays Febrile neutropenia=6 delays Neutropenia=2 delays Dose reduction=15 patients (50%) on 17 occasions (largest in cycle 5) due to: Haematological toxicity=8 reductions Neurological toxicity=2 reductions Gastrointestinal toxicity=1 reduction Other toxicities=3 reductions	NR

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
			Administrative reasons=3 reductions	
Zaja 2006[85]	NR	Modified R-CHOP (R-CCOP) Discontinuation=27.6%, due to: No response/progression=8 patients AEs=2 patients	NR	Grade 3-4 neutropenia=86%
Rigacci 2006[86]	R-CHOP-14 with G-CSF Median RDI=93%	92% completed planned 6 cycles Therapy related deaths=1 patient	1 patient (4%) changed to R-CHOP-21 due to toxicity 1 patient (4%) changed to MACOP-B (more intensive treatment) due to lack of response and good PS 6% of cycles were delayed in 8 patients (31%)	Grade 3-4 neutropenia=19%
Niitsu 2006[87]	NR	NR	CyclOBEAP Main reason for delay=bone marrow suppression	Grade 3 toxicity; Leukopenia=21.6% Neutropenia=19.6% Anaemia=39.2% Thrombocytopenia=43.1% Grade 4 toxicity; Leukopenia=62.7% Neutropenia=64.7% Anaemia=15.7% Thrombocytopenia=15.7% Grade 3-4 mucositis=10.8%
Niitsu 2006[88]	NR	NR	NR	R-CMD Grade 3-4 haematological toxicity=63.3% Grade 4 neutropenia=35% Grade 3-4 WBC=32%
Desch 2005[89] (abstract only)	R-CHOP <60 Dose intensity 95%	NR	NR	NR
	Rituximab then standard-dose CHOP CT >60 94% p=0.58	NR	NR	NR
Federico 2005[90] (abstract	R-COMP Median cycles 8, range 1 Dose intensity 87%	3 patients were withdrawn due to reduced LVEF.	8% were delayed by haematological or hepatic toxicity for a median of 7 days (range 0 to 25)	Grade 3 or 4 neutropenia in 29% of cycles Febrile neutropenia in 4%.

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
only)				
Monfardini 2005[91]	Vinorelbine and prednisone Median cycles per patient=4 (range 1-8)	NR	Delays=13.3% of patients by 1 week	Grade 3 neutropenia=10%
Rodriguez 2005[93] (abstract only)	NR	NR	NR	R-CHOP Neutropenia,=6% Anaemia=13%
Cervetti 2003[95]	NR	NR	NR	P-VBECDNX Grade 3 neutropenia=14%
Bernardi 2003[97] (abstract only)	CHOP/CEOP or CVP Patients with IADL <5 and patients >80 received 75% of standard dose	NR	NR	G3 Infection=16%
Gregory 2003[96]	CHOP-14 plus G-CSF All patients Completed all 6 cycles=86% ≥5 cycles=91%	NR	85% of cycles were on time and at full dose Reduced dose=15% of cycles	Grade 4 neutropenia=52% Other grade 3-4 haematological AE=17% Grade 3-4 anaemia=20% Any grade 3-4 toxicity=53%
	CHOP-14 plus G-CSF ≥60 Completed all 6 cycles=75% ≥5 cycles=85%	NR	80% of cycles were on time and at full dose	Grade 4 neutropenia=70% Other grade 3-4 haematological AE=23%
	CHOP-14 plus G-CSF <60 NR	NR	NR	Grade 4 neutropenia=37% Other grade 3-4 haematological AE=11%
Angrilli 2002[99] (abstract only)	NR	D-VICEMB Four patients in CR suspended treatment after five courses 4 patients in partial response refused treatment after 4/5 cycles 2 patients received only 2 cycles due to progressive disease	NR	NR
Martino 2002[100]	CCOP Median cycles per patient=6 (range 2-8) 39% of patients received <6 cycles	Deaths=4 patients (2 patients sudden death, 1 patient severe febrile illness, 1 patient multiorgan failure) Other discontinuation=9 patients (1 patient oral mucositis, 1 patient loss	36% of cycles delayed in 67% of patients. Mostly due to neutropenia	Grade 3-4 neutropenia=64% Grade 3-4 hair loss=24%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		from follow-up, 7 patients disease progression)		
Zinzani 2001[101]	NR	NAEPP Discontinuation=10%, due to progression	NR	No grade 3-4 toxicities ≥10%
Lichtman 2001[102]	TNOP Mean course per patient=4.5	NR	42.3% of patients had delayed treatment (17 cycles)	15.4% of patients experience severe or life-threatening events Grade 3-4; Gastrointestinal toxicity=15.4% Asthenia=19.2%
NHL – Indolent				
Raty 2012[103]	NR	Alternating R-CHOP/R-AraC Withdrew consent=4% Other discontinuation=17% (in CR/PR) due to fatigue/toxicity	Dose reductions=2-35% of patients	Grade 4 neutropenia=33.3% (44.4% after maintenance) Grade 3 infection=20%
Houot 2012[104]	NR	RiPAD+C Discontinuations=10% due to severe toxicity 8% did not receive first 4 cycles, due to: Progressive disease=5 patients Lethal toxicity=1 patient Refusal=1 patient Reasons for not continuing to 6 cycles (10 patients); Insufficient response=5 patients Toxicity=34 patients (incl. 1 death)	NR	Grade 3: Neurotoxicity (peripheral neuropathy)=18% Lung toxicity=13% One toxicity-related death
Jerkeman 2011[105] (abstract only)	LEN plus R-B Median cycles per patient=6.5 (max. 10)	NR	NR	Grade 3-4 AE occurrences=14
Magni 2011[106]	NR	NR	NR	Ofatumumab, bendamustine and dexamethasone Grade ≥3 AE: Neutropenia=10.5% Febrile neutropenia=10.5%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Ruan 2010[107]	NR	NR	NR	RT-PEPC Grade 3-4 Neutropenia=64% Thrombocytopenia=18% Community-acquired pneumonia/upper respiratory illness=18% Febrile neutropenia=18% Grade 3 infection=23%
Visani 2008[108]	R-COMP-21 RDI=83%		17% delayed due to haematological toxicity	Neutropenia=26% (of cycles) Any grade3-4 WHO toxicity=15%
Case Jr 2007[109]	R-CHOP with filgrastim 64% received all 6 cycles at full dose on schedule 87% received all 6 cycles at full dose >60 100% received filgratism RDI=91% ≤60 80% received filgratism RDI=93%	Reasons for discontinuation: Investigator decision=14% AEs=8% Other=10% (similar between age groups)	51% had no cycle delays ≥7 days Main reasons for modification; Scheduling=31.3% Unrelated medical conditions=24.1% Neutropenia=22.9%	Any grade 3-4 AE=67% Neutropenia=26% Febrile neutropenia=14%
Fabbri 2007[110]	Low dose fludarabine plus cyclophosphamide Median cycles per patient=4 (range 2-4)	Discontinuation=7 patients (5 after 3 cycles, 2 patients after 2 cycles), due to: Patient decision=3 patients Infection=2 patients Lack of response=2 patients	No delays or dose reductions	Grade 3-4 toxicity; Haematological=28% Neutropenia=16%
NHL – Mixed or undefined				
Mizoroki 2006[112]	VEPA/FEPP 47% of patients completed therapy	Discontinuation due to: Progressive disease=20% Toxicity=16%		Leukopenia=98% Anaemia=44% Thrombocytopenia=20%
Gimeno 2011[111]	R-CMyOP Median cycles per patient=5 (range 1-6)	Deaths=11 patients (4 patients infectious complications, 6 patients lymphoma, 1 patient hepatocellular carcinoma)	Delayed cycles=25.7% (of patients) Vincristine dose reduction=40%	Grade 3-4 toxicity; Granulocytopenia=54.2% Thrombocytopenia=25.7% Anaemia=20%
Bocchia 2003[113]	NR	Mini-FLEC Death=50%, due to disease	No dose reductions 4% of cycles delayed by 1 week	Grade 3-4 neutropenia=50%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		progression		

NHL=non-Hodgkin's lymphoma; AE=adverse event; HR=hazard ratio; CR=complete response; IADL=Instrumental Activities of Daily Living; PS=performance status; RDI=relative dose intensity; WHO=World Health Organisation;

CCNU=1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine); CCOP=pegylated liposomal doxorubicin, vincristine, cyclophosphamide and prednisone; CEMP=cisplatinum, etoposide, mitoxantrone, prednisone; CEOP=cyclophosphamide, vincristine, epirubicin and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; CMD=irinotecan, mitoxantrone and dexamethasone; COP-X=liposomal daunorubicin, cyclophosphamide, vincristine and prednisone plus G-CSF; CyclOBEAP=doxorubicin, cyclophospamide or etoposide, vincristine, prednisone, with or without bleomycin; DA-POCH-R=dose-adjusted infusional cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy with rituximab; D-VICEMB=cyclophosphamide, mitoxantrone, etoposide, bleomycin, vinblastine and dexamethasone; EMP=etoposide, mitoxantrone and prednisone; FEPP=vindesine, etoposide, procarbazine, prednisone; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor; LEN plus R-B=lenalidomide, bedamustine and rituximab; Mini-FLEC=epirubicin, fludaribine, cyclophosphamide; NAEPP=vinorelbine, epirubicin, prednisone; NPLD=non-pegylated liposomal doxorubicin; P-VBECDNX=etoposide, cyclophosphamide, DaunoXome, vincristine, bleomycin, prednisone; R-AraC=cytarabine plus rituximab; R-BM=rituximab, mitoxantrone and bendamustine; R-CCOP=modified R-CHOP (pegylated liposomal doxorubicin, vincristine, cyclophosphamide and prednisone); R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CMD=rituximab, irinotecan, mitoxantrone and dexamethasone; R-CMyOP=NPLD, cyclophosphamide, vincristine and prednisone; R-CNOP=cyclophosphamide, mitoxantrone, vincristine and prednisone plus rituximab; R-CVEP=rituximab, cyclophosphamide, etoposide, prednisone, procarbazine, vorinostat; R-CVP=cyclophosphamide, vincristine and prednisone plus rituximab; R-COMP=cycolphosphamide, vincristine and prednisone plus rituximab; R-GemOx=gemcitabine and oxaliplatin plus rituximab; RiPAD+C=rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil; R-mini-CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab; R-THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine, and prednisolone plus rituximab; R-VNCOP-B=etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, and bleomycin, rituximab; RT-PEPC=prednisone, etoposide, procarbazine and cyclophosphamide plus rituximab and thalidomide; THP-COP=tetrahydropyranyl adriamycin–cyclophosphamide, vincristine and prednisolone; TNOP=thiotepa, novantrone [mitoxantrone], vincristine and prednisone; VEPA=vincristine, cyclophosphamide, doxorubicin, prednisone; NR=not reported

9.4 Geriatric assessment and quality of life

Three studies[58,75,97]reported information relating to CGA. Details are presented in Table 17.

Comprehensive geriatric assessment

Three studies[58,75,97] presented data on the use of CGA tools. Bernardi et al[97] used CGA to determine the regimen patients received based on CGA results. Two studies used the tools to categorise patients into appropriate groups for comparison of outcomes. A range of tools were used across the studies: Activities of Daily Living (ADL), IADL, geriatric depression, mini-mental status (MMS), and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).

Table 17 Geriatric assessment and quality of life, single cohorts

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
Bernardi 2003[97] (abstract only)	ADL IADL	To categorise patients at enrolment in order to determine treatment regimen	NR	NR
Tucci 2009[75]	ADL CIRS-G	To categorise patients into fit/unfit	NR	NR
Spina 2012[58]	ADL IADL Geriatric depression MMS (mini mental state) CIRS-G	As baseline data and to categorise into fit/unfit	NR	NR

ADL=Activities of Daily Living; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; IADL=Instrumental Activities of Daily Living; MMS=mini-mental status; NR=not reported

9.5 Summary and discussion

The 63 studies[53-115] included in the review have provided an abundance of evidence; however, the studies were predominantly small and heterogeneous, which did not allow for useful synthesis of the studies. Clinical consensus suggests that the data from single-cohort studies are difficult to interpret in any meaningful way; however, the data have been included in this report for completeness and to show the extent of the evidence base.

10 RETROSPECTIVE DATA

A total of 22 studies[123-144] (reported in 24 publications[123-146]) analysed retrospective data included in the review. Details are presented in Table 18.

10.1 Study characteristics

The retrospective studies were categorised into those that focussed on patients with aggressive disease, and those that focussed on mixed or undefined patient populations. Across the studies, there were often gaps in the reporting of study methods, characteristics and baseline data, such as PS or IPI score.

10.1.1 Aggressive disease

Nineteen retrospective studies[123-141] focussed on patients with aggressive disease. The majority of studies were single centre, and reporting of methodology was usually poor. The subtype of NHL was predominantly DLBCL; however, the studies were very heterogeneous in terms of stage of disease, PS, IPI (or equivalent) score, median age, and the treatment regimens investigated. The definition or cut-off age for 'older' ranged from ≥53 to ≥80 years. Some of the studies describe data collected during the 1990s, and therefore could be considered out of date for the current review.

10.1.2 Mixed or undefined disease

Three retrospective studies[142-144] focussed on mixed or undefined patient populations. Again, the populations across the studies were heterogeneous and vary in study design, treatment type and baseline characteristics.

Table 18 Study characteristics, retrospective studies

Study	Details	Population summary	Intervention	Baseline	Outcomes/purpose	Conclusions
NHL – Aggressive disease						
Boslooper 2012[123] (abstract only)	Multicentre The Netherlands Follow-up 13 months (range 1-78) [31 months for survivors] 2005-2011	DLBCL Stage I=19%, II-stage IV=71%, NR=10% First-line Aged >75	R-CHOP=84 R-CHOP plus RT (n=13)	Median age: 81 years (75-96) Male: 43% aaIPI: HI-H=43%	To assess efficacy, tolerability and safety of standard intensive rituximab-containing therapy	Age only is a poor indicator to differentiate between fit elderly patient who will benefit from intensive therapy and frail patients. Other strategies for patient selection, such as the implication of a CGA, should be further evaluated in very elderly patients with DLBCL
Bowcock 2012[124]	Single centre UK 2000-2010	DLBCL=94% BL=6% Stage 3/4=86% Aged ≥70	Intensive (CHOP, R-CHOP, CODOX-M/IVAC) (n=22) or Modified intensity chemotherapy (PACEBP, PMitCEBO, R-CVP, CIDEX) (n=29)	Median age: Intensive=76 years (70-89) Modified=78 years (70-83) Male: 33.3% (out of 30 patients)	To evaluate toxicity and efficacy	In summary, we show that elderly patients with aggressive B-cell lymphoma and very poor PS can achieve good eventual OS. Toxicities can be ameliorated with steroid pre-phase and initial chemotherapy dose reduction. In the moribund, staggered initial treatment may be better tolerated
Hasselblom 2012[125]	Single centre Sweden Follow-up 29-46 months 1997-2000 (pre-rituximab era), 2006-2009 (post-rituximab introduction) Funding: FoU Vastra Gotalandsregion en and the Swedish Medical Society	DLBCL Aged ≥80	Pre-R: CHOP or CNOP(n=30) Post-R: R-CHOP (n=40)	Median age: Pre-R=84 years (80-89) Post-R=85 years (80-91) Male: Pre-R=50% Post-R=43% PS ≥2: Pre-R=47% Post-R=45%	To evaluate whether the introduction of immunochemotherapy influenced survival in an unselected cohort of very elderly patients	In conclusion, moderately reduced R-CHOP is tolerable and effective for a considerable number of very elderly patients with DLBCL, and high age by itself should not be a reason for excluding a patient with DLBCL from such treatment
Li 2012[126]	Multicentre China Follow-up 86	DLBCL First-line Aged>60	CHOP (n=240) R-CHOP (n=197)	Median age: 53 years Male: CHOP=56.3%	To evaluate the 10 years' follow-up of the efficacy in Chinese patients	The results of this large-scale study suggested that R-CHOP provided a greater survival

	months (10-146) 1997-2008 Funding: Shanghai Lymphoma Research Group	CHOP=35%, R-CHOP=30.5% (Overall=32.3%)		R-CHOP=49.7% ECOG 0-1: CHOP ≤60=54.6% CHOP >60=22.9% R-CHOP ≤60=61.9% R-CHOP >60=19.8% ECOG 2-3 CHOP ≤60=10.4% CHOP >60=12.1% R-CHOP ≤60=7.6% R-CHOP >60=10.7%	receiving CHOP or R-CHOP as the initial treatment for DLBCL	benefit in the initial treatment of DLBCL. As for the patients with extranodal lymphoma, R-CHOP was also a good choice as first-line treatment. Extranodal disease seems to be an independent good prognostic factor in rituximab era
Lin 2012[127]	Single centre Taiwan 2003-2010	DLBCL Stage: I/II=48.3% III/IV=51.7% First-line Aged >60 (>70=63.1%)	COP or R-COP (n=179) CHOP or R-CHOP (n=129) ('Other'=25)	Median age: 73 Male: 55 ECOG All: <2=69.7% ≥2=30.3% IPI All: L-LI=52.9% HI-H=47.1%	To review 333 DLBCL patients aged >60 years who were diagnosed between January 2003 and December 2010 to evaluate the difference between different treatment regimens	In conclusion, our results showed that patients with younger age or better PS received more intensive treatment. The treatment regimen was not different between patients with lower and higher CCI. Rituximab-containing regimens improved the outcome of elderly patients with DLBCL
Jo 2012[128] (abstract only)	Single centre South Korea Follow-up 22.9 (4.5-58.7) 2007-2012	DLBCL Stage: I/II=36.4% III/IV=63.6% Aged >65 (>80=7.6%)	R-CHOP (n=118)	Median age: 72 (65-85) Male: ECOG PS: <2=100% IPI=L=26.3% LI=17.8% HI=21.2% H=34.8%	To assess the efficacy and safety of R-CHOP with reduced doses of cyclophosphamide and doxorubicin by 25% in elderly patients with DLBCL	The R-CHOP chemotherapy with reduced dose of cyclophosphamide and doxorubicin did not appear to attenuate the efficacy of R-CHOP chemotherapy in the elderly patients when compared with the original report (Coiffier et al, NEJM 2002). However, toxicities still matter despite upfront dose reduction. Tailored strategies or other regimens with better toxicity profiles are in need for these patients
Meguro 2012[129]	Single centre Japan Follow-up ≥70=36 months, <70=41 months 2003-2010	DLBCL Stage: (≥70/<70) I=14.8%/34.8% II=40.9%/17.4% III=11.5%/10.1%	R-70%CHOP (70% dose of CHOP plus rituximab) ≥70, n=61 Full dose R-CHOP <70, n=69	Median age: ≥70=76 <70=61 (50-69) Male: ≥70=60.7% <70=59.4%	To investigate whether dose reduction still has a role in the treatment of DLBCL for the specific subgroup of patients aged ≥70 years	3-year PFS with R-70%CHOP for patients aged ≥70 years was not significantly worse than that with full-dose R-CHOP for younger patients, suggesting that R-70%CHOP might be a

		IV=32.8%/37.7% First-line Aged ≥70=46.9%		Age adjusted IPI ≥70 L=26.2% LI=32.8% HI=27.9% H=13.1% <70) L=21.7% LI=36.3% HI=20.3% H=20.3%		reasonable choice for patients with DLBCL aged ≥70 years
Stephens 2012[130] (abstract only)	Single centre USA 2002-2011	DLBCL Stage: III/IV=86% First-line Aged >65 (≥75=41%)	DA-REPOCH (n=69)	Median age: (range 65-92) PS: ≥2=43% aaIPI: ≥2=77%	NR	In this retrospective study, toxicity is increased with DA-REPOCH in patients ≥65 with DLBCL, compared with published results in a younger population. Age ≥75, impaired CrCl, and poor PS are associated with increased risk of dose reductions and delays, although age and dose reductions do not appear to impact ORR and PFS
Van de Schans 2012[131]	Multicentre The Netherlands 1997-2004 Funding: Dutch Cancer Society	DLBCL Ann Arbor: II=38% III=26% Aged ≥75 (80-84=34%, >85=18%)	CHOP-like chemotherapy (n=179) 'Milder regimen' or no chemotherapy (n=208)	Median age: 81 years Male: ECOG PS: 0-1=40% 2-3=26% Unknown=34%	To investigate treatment, treatment tolerance, motives for suboptimal treatment and outcome in elderly patients, aged >75 years, with advanced-stage DLBCL	Standard therapy was applied less often in elderly patients with a subsequent independent negative impact on survival. Furthermore, high toxicity rate and the impossibility of the majority of patients to complete treatment were seen. This implies that better treatment strategies should be devised including a proper selection of senior patients for this aggressive chemotherapy
Griffiths 2011[132]	Multicentre USA 2.3 years 1999-2005 Funding: Genetech Inc.,	MCL Stage: I-II=20.1% III-IV=74.6% Unknown=5.3% First-line Aged ≥65	CHOP OR CNOP (n=230) R-CHOP or R-CNOP (n=408)	Median age: 74 years Mean age=75 years Male: All patients=67.4%, CHOP=63.6% R-CHOP=69.5% PS:	To examine the survival impact of adding rituximab to first-line chemotherapy in a cohort of older MCL patients treated in routine clinical practice	We conclude that first-line chemotherapy including rituximab is associated with significantly improved survival in older patients diagnosed with MCL

	Outcomes Insights Inc.	(>80=22.9%)		0=84.8% ≥1=15.2%		
Guo 2011[133]	Single centre China Follow-up 49.5 (29.2-90.8) Funding: The 11th Five-Year Plan of the People's Liberation Army (PLA) Fund	DLBCL=95.5% T-cell enriched DLBCL=4.5% Stage: I-IIA=18.2% IIB-IVB=81.8% Aged >75	R-CHOP with liposomal doxorubicin (n=22)	Median age: 83.5 years (76-87) Male: 95.5 IPI: L-LI=40.9% HI-H=59.1%	To evaluate the efficacy and safety of individualised liposomal doxorubicin-based treatment in elderly patients with NHL and poor general health	Individualised liposomal doxorubicin-based chemotherapy is effective and safe for elderly patients with NHL
Hoffmann 2011[134] (abstract only)	Single centre USA	DLBCL Aged ≥65 (≥80=20%) Split R-CHOP given to those patients considered too frail for standard chemotherapy	R-CHOP=76% R-HyperCVAD=5% R-CVP=2% 'split R-CHOP' regimen=17% (n=41)	Median age: 74 years (65-86)	NR	Our data reveal interesting findings about elderly patients treated for DLBCL. PFS and OS in general are poor as has been reported by others. In our data set, patients >80 years considered fit for standard chemotherapy, had a shorter PFS then fit patients between 65 to 80 years
Hsu 2011[135] (abstract only)	Single centre Australia Follow-up 28.1 (13-92.7) 2000-2010	DLBCL First-line=32% Aged >70	CEEP +/- rituximab (73%) +/- G-CSF (50%) (n=22)	Median age: 78.5 years (71-85) Male: 45.5% ECOG ≥2=23% RIPI >=3=55%	To look at the efficacy and tolerability of CEEP, a lower intensity regimen for elderly patients with newly diagnosed or relapsed DLBL whom are deemed inappropriate for CHOP-based chemotherapy	CEEP +/- rituximab chemotherapy can be administered to elderly patients with significant comorbidities
Kobayashi 2011[136]	Single centre Japan Follow-up 28 months 2001-2008	DLBCL Ann Arbor: III-IV=40% Aged >65 (>80=16%)	CHOP-based=90% (the rest may include RT) (n=80)	Median age: 73 years (66-90) Male: 54 ECOG ≥2=30% IPI HI-H=46%	To evaluate the correlation between comorbid medical status and clinical outcome among elderly patients with DLBCL	Among elderly DLBCL, high CCI was independently associated with worse outcome. Novel discrete strategies for these deteriorated patients are therefore warranted
Taoka 2010[137]	Single centre Japan 2005-2009	PCNSL (DLBCL of CNS) Aged ≥60	Methotrexate-containing chemotherapy (n=17)	Median age: 67 years (58-78) Male: 58.8 PS	To assess the efficacy, acute toxicity, and delayed neurotoxicity of intermediate-dose	In conclusion, a 2-year OS rate of 61% without acute or delayed therapy-related neurotoxicities such as dementia was achieved

		(or ≥55 if poor PS)		0-1=100%	methotrexate-containing chemotherapy	by a nonradiation-containing, repeated intermediate-dose methotrexate regimen in Japanese patients. Because of its efficacy and toxicity balance, this may be one of the protocols of choice for elderly patients with PCNSL, leaving a question of rituximab incorporation
Giordano 2007[138] (abstract only)	Single centre Italy Follow-up 18.5 (8-34)	DLBCL Stage IV=50%	R-CCOP (n=20)	Median age: 76 years (67-87) Male: 50% IPI: HI=25% H=40%	Liposomal doxorubicin instead of conventional doxorubicin in CHOP regimen to reduce myocardic toxicity and enhance doxorubicin uptake in tumour mass in B-NHL of elderly patients with comorbidity, advanced stage and aggressive disease	In elderly B-NHL patients with advanced stage of disease and comorbidity, R-CCOP seems to be safe and feasible and effective. The use of R-CCOP seems not to impair response to second-line treatment in nonresponding patients. Nevertheless, these data need confirmation in a larger cohort of patients. The low PFS probably is due to particularly unfavourable clinical characteristics of treated patients
Italiano 2005[139]	Multicentre France Follow-up 23 months 2001-2003	B Cell DLBCL=79% Mantle cell=12.5% Follicular=8.5% I=8.5% II=21% III=33% IV=37.5% Second-line Aged >80	R-CHOP (n=24)	Median age: 83 years (80-88) Male: 41.5 ECOG PS: 0=8.3% 1=50% 2=33.3% 3=8.3% aaIPI: L=4% LI=21% HI=8.5% H=12.5% NA=54%	To retrospectively assess the safety and efficacy of R-CHOP in patients >80 years old	Age alone should not be used as a reason to deny patients with NHL an adapted and potentially curative treatment
Enting 2004[140]	Single centre US, Follow-up 17 (4-30) 2001-2003	PCNSL Second-line Recurrent or refractory Aged ≥53	Rituximab and temozolomide (n=15)	Median age: 69 years (53-78) Male: 33.3% KPS: Median=70 (50-100)	To evaluate the efficacy of a combination of rituximab and temozolomide for recurrent or refractory	This combination merits further study and provides a reasonable therapeutic alternative for older patients with progressive PCNSL

	Funding: Genentech, Inc., Schering-Plough Research Institute Charles H. Revson Foundation, Dutch Cancer Society				PCNSL	
Jabbour 2004[141]	Single centre France 1994-2002	DLBCL=90% PTCL=10% Stage: I=34% II=23% III=12% IV=31% First-line=98% Aged >60	CHOP/CHOP-like (n=94)	Median age: 70 years (60-90) Male: 58.5 PS: 0=50% 1=30% 2=15% 3=5%	We retrospectively reviewed the clinical features of patients >60 treated at our centre who did not achieve a sustained complete remission after first-line therapy	Conventional-dose second-line chemotherapy yields disappointing results in elderly patients with aggressive lymphomas
NHL – Mixed or undefined						
Horn 2012[142]	Phase II Single centre Germany 2003-2010 Funding: Deutsche Krebshilfe, and Mundipharma	B cell DLCL=75% Follicular=20% Burkitt=5% Stage: III/IV=60%	Rituximab + bendamustine (n=20)	Median age: 72 years (51-86) Male: 60 KPS: median 55% (40-90) IPI: ≤2=25% ≥3=75%	To analyse the safety and efficacy of rituximab plus bendamustine in elderly and frail patients with aggressive B-cell NHL	Rituximab plus bendamustine is a feasible and safe therapy option in patients with aggressive B-cell NHL not qualifying for R-CHOP but needs to be further assessed in larger subsequent trials, which are currently under way
Lignon 2010[143]	Single centre France Follow-up 23 months 2003-2008	DLBCL=46% Follicular=33% Other=21% Ann Arbor: I-II=20% III-IV=80% Second-line Aged ≥60=53% (>70=20)	R-DHAX (n=91)	Median age: 60 years (range 28-82), 51 years (range 28-59), 66 years (range 60-70), 74 years (range 71-82) Male: 63% PS: 0-1=83% 2=10% 3=5% 4=2%	To analyse a large series of 91 patients presenting with relapsed/refractory B-cell NHL treated by DHAX combined with rituximab in a single institution between 2003 and 2008	R-DHAX is an efficient regimen in patients with relapsed/refractory B-cell NHL even in elderly patients if haematological toxicities are closely managed
Sehn 2005[144]	Multicentre Canada 1999-2002	DLBCL III-IV (or with 'B' symptoms)	CHOP (or CHOP-like: ACOP=32% /	Median age: 64 years (19-86) Male:	To assess the impact of this combination therapy on adult patients with	The addition of rituximab to CHOP chemotherapy has resulted in a dramatic

	Funding: Turner Family Lymphoma Outcome Unit Fund	Aged ≥60=58%	COPA=15% / ECV=3%) (n=140) R-CHOP (or CHOP-like regimen-2%) (n=152)	CHOP=57% R-CHOP=61% PS: CHOP >1=47% R-CHOP >1=40%	DLBCL in the province of British Columbia	improvement in outcome for DLBCL patients of all ages in the province of British Columbia

BL=Burkitt lymphoma; CNS=central nervous system; DLBCL=diffuse large B-cell lymphoma; MCL=mantle cell lymphoma; NHL=non-Hodgkin's lymphoma; PCNSL=primary central nervous system lymphoma; PTCL=peripheral T-cell lymphoma;

aaIPI=age-adjusted International Prognostic Index (L=low risk; LI=low-to-intermediate risk; HI-high-to-intermediate risk; H=high risk); CCI=Charlson Comorbidity Index; CGA=comprehensive geriatric assessment; CR=complete response; ECOG=Eastern Cooperative Oncology Group; EFS=event-free survival; KPS=Karnofsky performance status; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PS=performance status;

ACOP=doxorubicin, cyclophosphamide, vincristine, and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; CIDEX=lomustine + idarubicin+ dexamethasone; CNOP=cyclophosphamide, mitoxantrone, vincristine and prednisolone; COP=cyclophosphamide, vincristine, and prednisolone; COPA=cyclophosphamide, vincristine, prednisone, and doxorubicin; DA-REPOCH=dose adjusted eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone, plus rituximab; G-CSF=granulocyte colony-stimulating factor; CODOX-M/IVAC= cyclophosphamide + doxorubicin + vincristinemethotrexate alternating cycles with ifosfamide + VP16 + cytarabine; PMitCEBO=prednisolone, mitoxantrone, cyclophosphamide, etoposide, vincristine, and bleomycin; R-CCOP=endoxan, vincristine, prednisone, liposomal doxorubicin plus rituximab; R-CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone plus rituximab; R-CNOP=cyclophosphamide, mitoxantrone, vincristine and prednisolone plus rituximab; R-COP=cyclophosphamide, vincristine, and prednisolone plus rituximab; R-CVP=cyclophosphamide, vincristine and prednisone plus rituximab; R-DHAX=dexamethasone, cytarabine, oxilaplatin plus rituximab; R-HyperCVAD=cyclophophamide, doxorubicin, vincristine, dexamethasone plus rituximab; RT=radiotherapy; NA=not available; NR=not reported

10.2 Efficacy evidence

Results for efficacy outcomes reported in the retrospective data studies are presented in Table 19.

10.2.1 Aggressive disease

Time-to-event outcomes were presented primarily as median PFS, or PFS rates at given follow-up periods, and EFS across a wide variety of treatment regimens. Some statistically significant results were reported: Hasselblom et al[125] reported statistically significantly better 3-year PFS with R-CHOP compared with CHOP alone in older patients (p=0.015). Similarly, Li et al[126] reported that for older patients, R-CHOP resulted in a statistically significantly higher median PFS than CHOP alone (p=0.009). Lin et al[127] reported that, although the addition of rituximab to COP/CHOP improves PFS in the general population, there was no significant difference in PFS between older and younger patients (p=381). Survival-related outcomes of median OS or survival rates at specific intervals were well reported.

10.2.2 Mixed or undefined disease

Two studies presented PFS-related data: Horn et al[142] reported a median PFS of 8.3 months for older patients, and Sehn et al[144] reported 2-year PFS of 44% for older patients compared with 60% for younger patients. Survival-related outcomes were reported by all three studies.[142-144] The 2-year OS was 66% for those aged 60-70 years and 36% for those aged >70 years in Lignon et al.[143] Results for 2-year OS for older versus younger patients for CHOP and R-CHOP were 42% versus 67%, and 73% versus 85%, respectively. Two studies presented data for ORR in older patients, which varied from 11%[142] to 72%/73%.[143]

Table 19 Efficacy outcomes, retrospective studies

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
NHL– Aggressive disease							
Bowcock 2012[124]	Intensive (22 patients) *of 23 patients, from earlier report	NR	NR	3-year OS=64% OS=48 months (12 to 99)*	NR	NR	NR
	Modified			3-year OS=14% OS=5 (0.5 to 126)			
	All patients (30 patients, from earlier report)			OS=39 months (8 to 123)			
Hasselblom 2012[125]	CHOP	3-year PFS=17%	p=0.015	3-year OS=17%	p=0.01	NR	NR
	R-CHOP	3-year PFS=41%		3-year OS=41%		NR	
	Curative CHOP	3-year PFS=27%	p=0.018	3-year OS=27%	p=0.0089	45%	p=0.06
	Curative R-CHOP	3-year PFS=70%		3-year OS=76%		76%	
	Palliative CHOP	NR	NR	OS=7 months	p=0.48	NR	NR
	Palliative R-CHOP	NR		OS=5 months		NR	
Li 2012[126]	All patients CHOP	Median 86 months; PFS=66.7%	p=0.015	Median 86 months; OS=70.2%	p=0.018	85%	p=0.003
	All patients R-CHOP	Median 86 months; PFS=81.5%		Median 86 months; OS=84.1%		94.4%	
	>60 CHOP	Median 66 months; PFS=52.5%	p=0.009	Median 66 months; OS=53.6%	p=0.011	NR	NR
	>60 R-CHOP	Median 66 months; PFS=80.7%		Median 66 months; OS=80.7%		NR	
	≤60 CHOP	NR	NR	OS=79.4%	p=0.428	NR	NR
	≤60 R-CHOP	NR		OS=85.5%		NR	
Lin 2012[127]	All patients	PFS=14.4 (9.8-19)	NR	OS=24.8 (15.8-33.8)	NR	NR	NR
	With rituximab	PFS=22.2 (7.3-37)	p=0.005 – abstract p=0.004 – text	OS=34.9 (13.2-30.4)	p=0.042	76.7%	p=0.002
	Without rituximab	PFS=9.9 – abstract =9.7 (6.7-12.7) – text		OS=21.8 (28.6-41.2)		68.9%	

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
	COP/R-COP	10.8 (7.6-13.9)	p<0.001	OS=14.4 (5.6-23.2)		63.1%	
	CHOP/R-CHOP	PFS=36.2 (14.1-58.4)		OS=62.9 (50-66.2) – table OS=62.9 (54.8-71) – text	p<0.001	88.4%	p<0.001
	COP	PFS=7.7	p<0.001	OS=11.6	p=0.013	NR	NR
	R-COP	PFS=15		OS=29.7		NR	
	CHOP	PFS=36.2	p=0.891	OS=62.9	p=0.934	NR	NR
	R-CHOP	PFS=37.6		OS=not reached (best OS)		NR	
	>70	PFS=12	p=0.381	19.3 (10.2-28.4)	p=0.112	NR	NR
	≤70	PFS=16.2		33.2 (11-55.3)		NR	
Meguro 2012[129]	R-70%CHOP in ≥70	3-year EFS=45% 3-year PFS=64%	EFS, p<0.05 PFS, p=0.43	3-year OS=58%	p<0.05	87%	p=0.65
	R-CHOP in <70 (50-69)	3-year EFS=70% 3-year PFS=72%		3-year OS=78%		84%	
Stephens 2012[130] (abstract only)	DA-REPOCH	17 months (6-43)	NR	NR	NR	67% (52-75)	NR
Jo 2012[128] (abstract only)	R-CHOP	2 year PFS=60.6%	NR	68.7%	NR	78%	NR
Van de Schans 2012[131]	All patients	NR	NR	5-year OS=18%	NR	NR	NR
	All patients CHOP-like			6-month OS=80% 5-year OS=31%			
	CHOP-like At least 6 cycles			6-month OS=97% 5-year OS=38%	HR compared to at least 6 cycles of CHOP-like chemotherapy; Less than 6 cycles=1.9		
	CHOP-like Less than 6 cycles			6-month OS=58% 5-year OS=22%			

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
					Milder regimen=1.6 No chemotherapy =4.7		
	'Milder regimen'			6-month OS=48% 5-year OS=12%			
	No chemotherapy			6-month OS=24% 5-year OS=4%			
Griffiths 2011[132]	CHOP	NR	NR	Median survival=27 months (20-31) 2-year survival=52%	p<0.001	NR	NR
	R-CHOP			Median survival=37 months (33-44) 2-year survival=63%			
Guo 2011[133]	R-CHOP with liposomal doxorubicin	1-year PFS=83.3% 3-year PFS=66.7% 5-year PFS=54.5%	NR	1-year OS=81.8% 3-year OS=59.1% 5-year OS=40.9%	NR	81.8%	NR
Hoffmann 2011[134] (abstract only)	"All treatments	PFS=12 months	NR	OS=24 months	NR	NR	NR
	Standard chemotherapy 65-80	PFS=16 months		NR			
	Standard chemotherapy ≥80	PFS=7 months		NR			
	Split R-CHOP	PFS=11.7 months		NR			
Hsu 2011[135] (abstract only)	10-month follow-up	NR	NR	NR	NR	77%	NR
	28.1-month follow-up	NR	NR	NR	NR		NR
Kobayashi 2011[136]	All patients	NR	NR	3-year OS=70%	NR	NR	NR
	IPI L-LI			3-year OS=90%	p<0.0001		
	IPI HI-H			3-year OS=45%			

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
	Low CCI			3-year OS=85%	p=0.0026	93%	p=0.0158
	High CCI (18%)			3-year OS=55%		64%	
Taoka 2010[137]	Methotrexate-containing chemotherapy	20 months 1-year PFS=80% (60-100) 2-year PFS=43% (14-73)	NR	36 months 1-year OS=100% 2-year OS=61% (34-88)	NR	100%	NR
Giordano 2007[138] (abstract only)	R-CCOP	34 months 50% (35.5-89.2)	NR	78% (58-100)	NR	NR	NR
Italiano 2005[139]	R-CHOP	EFS 50%	NR	2 year 76%	NR	79%	NR
Enting 2004[140]	Rituximab and temozolomide	Responders; PFS=7.7 months (2-22+) All patients; PFS=2.2 months (0-22+)	NR	OS=14 months	NR	53% (30-75)	NR
Jabbour 2004[141]	IPI 0	NR	NR	3-year OS=69% (51-87) 5-year OS=64% (44-79)	NR	NR	NR
	1	NR	NR	3-year OS=47% (24-67) 5-year OS=34% (13-55)	73%		
	2	NR	NR	3-year OS=20% (5-40) 5-year OS=0			
	3	NR	NR	3-year OS=0 5-year OS=0			
NHL – Mixed of undefined							
Horn 2012[142]	Rituximab +	8.3 months (2.8-NR)	NR	19.4 months (4.6-NR)	NR	11%	NR

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
	bendamustine						
Lignon 2010[143]	All patients	NR	PFS – significantly influenced by age; p=0.04	NR	NR	75%	NR
	<60			NR		NR	
	60-70			2-year OS=66%		73%	
	>70			2-year OS=36%		72%	
Sehn 2005[144]	All patients CHOP	2-year PFS=51%	NR	2-year OS=52%	NR	NR	NR
	≥60 CHOP	2-year PFS 44%	NR	2-year OS=42%	NR		
	<60 CHOP	2-year PFS=60%		2-year OS=67%			
	All patients R-CHOP	2-year PFS=69%	NR	2-year OS=78%	NR		
	≥60 R-CHOP	2-year PFS=68%	p=0.68	2-year OS=73%	p=0.99		
	<60 R-CHOP	2-year PFS=70%		2-year OS=85%			

CCI=Charlson Comorbidity Index; CI=confidence interval; NHL=non-Hodgkin's lymphoma; DFS=disease-free survival; EFS=event-free survival; HR=hazard ratio; IPI=International Prognostic Index (L=low risk; LI=low-to-intermediate risk; HI-high-to-intermediate risk; H=high risk); ORR=overall response rate; PFS-progression-free survival; OS=overall survival; TTP=time to disease progression; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; COP=cyclophosphamide, vincristine, and prednisolone; DA-REPOCH=dose adjusted eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone, plus rituximab; R-CCOP=endoxan, vincristine, prednisone, liposomal doxorubicin plus rituximab; R-CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone plus rituximab; R-COP= cyclophosphamide, vincristine, and prednisolone plus rituximab; NR=not reported

10.3 Tolerability evidence

Outcomes relating to tolerability are presented in Table 20. Across the studies, outcomes were not well reported.

10.3.1 Aggressive disease

One study[125] reported on treatment RDI, which was 95% for CHOP and 86% for R-CHOP. Discontinuations and withdrawals were reported by two studies, with the main reason for treatment discontinuation being AEs. Dose modifications and/or delays were reported by five studies. Adverse events were better reported, with high rates of haematological toxicity at grade 3-4. Three studies also reported treatment-related deaths, which ranged from 1 patient,[125] to 33% of patients aged >80 years.[134]

10.3.2 Mixed or undefined disease

There were no data reported for treatment completion or dose intensity, or for withdrawals and/or discontinuations. Lignon et al,[143] reported modifications or treatment delays, which ranged between 20% and 30% across all age groups. Two studies[142,143] presented AE data, which showed high rates of haematological toxicity.

Table 20 Tolerability, retrospective studies

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
NHL – Aggressive disease				
Bowcock 2012[124]	NR	NR	Intensive – PS4 (moribund*) First dose: 30-59%=6 patients 60-84%=1 patient	Grade 3-4 neutropenia=100% Myocardial infarction=1 patient (14%) Tumour lysis=1 patient (14%)
	NR	NR	Intensive – PS4 (other) First dose: 60-84%=1 patient ≥85%=1 patient	Grade 3-4 neutropenia=100%
	NR	NR	Intensive – PS3 Intensive – PS3 First dose: 60-84%=3 patients ≥85%=10 patients	Grade 3-4 neutropenia=100%
	NR	NR	NR	Modified Grade 3-4 neutropenia=100%
Hasselblom 2012[125]	Curative CHOP RDI=0.95 (0.61-1.14)	Discontinuations=3 patients (27%), due to non-fatal toxicity	NR	Toxic death=1 patient (cardiac failure)
	Curative R-CHOP RDI=0.86 (0.6-1.29)	Discontinuations=4 patients (19%), due to non-fatal toxicity		Toxic death=2 patients (septicaemia)
Li 2012[126]	CHOP Median cycles per patient=6 (4-8)	NR	NR	NR
	R-CHOP Median cycles per patient=6 (4-8)			
Meguro 2012[129]	R-70%CHOP ≥70 Average cycles per patient=5.4	NR	NR	Leukocytopenia: Grade 3=29.5% Grade 4=60.7% Anaemia: Grade 3=11.5% Grade 4=4.9%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				Grade 3-4; Fever=26.2% Constipation=13.1%
	R-CHOP<70 Average cycles per patient=6.2			Leukocytopenia: Grade 3=18.8%, p=0.15 Grade 4=76.8%, p<0.05 Anaemia: Grade 3=15.9%, p=0.46 Grade 4=5.8%, p=0.82 Grade 3-4: Fever=23.2%, p=0.69 Constipation=2.9%, p<0.05
Stephens 2012[130]	NR	NR	DA-REPOCH Dose reductions=48% patients Dose delay=39% patients	13% died of toxicity
Jo 2012[128]	NR	NR	R-CHOP 34.7% required dose reductions	Neutropenia=46.6% Thrombocytopenia=10.2% Febrile neutropenia=27.1%
Van de Schans 2012[131]	All patients CHOP-like 52% completed at least 6 cycles 73% could not complete the scheduled standard treatment	NR	Initial dose reduction=12% Dose reduction during treatment=20% Dose delays=22% Change to milder regimen=9% Main reason (53%)=toxicity	Any grade 3-4 toxicity=67%
	NR	NR	NR	75-79 CHOP-like Any grade 3-4 toxicity=62%
	NR			80-84 CHOP-like Any grade 3-4 toxicity=73%
	NR			≥85 CHOP-like Any grade 3-4 toxicity=85%
	NR			'Milder regimen' Any grade 3-4 toxicity=40%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Guo 2011[133]	R-CHOP with liposomal doxorubicin Mean dose 143.6 mg/patient liposomal doxorubicin Average cycles per patient=3.6	NR	NR	NR
Hoffmann 2011[134]	NR	NR	NR	All treatments Treatment-related deaths=17%
	NR	NR	NR	Standard chemotherapy 65-80 years Treatment-related deaths=14%
	NR	NR	NR	Standard chemotherapy ≥80 years Treatment-related deaths=33%
	NR	NR	NR	Split R-CHOP Treatment-related deaths=14%
Hsu 2011[135]	NR	NR	NR	CEEP + R Haematological=73% (febrile neutropenia=41%)
Taoka 2010[137]	NR	NR	NR	Methotrexate-containing chemotherapy Grade 3: Thrombocytopenia=12% Neutropenia=12% Anaemia=12% Cognitive disturbance=24% Grade 3-4 AST and ALT=12% Grade 4: Thrombocytopenia=12% Neutropenia=24%
Italiano 2005[139]	NR	NR	R-CHOP 92% received dose reductions-doxorubicin	NR
Enting 2004[140]	NR	Rituximab and temozolomide	NR	Grade 3 thrombocytopenia=27%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		Discontinuation=2 patients, due to grade 3 thrombocytopenia		
NHL – Mixed or undefined				
Horn 2012[142]	NR	NR	NR	Rituximab plus bendamustine: Haematological=25% (Anaemia 10%) Non-haematological=20% (infection 10%)
Lignon 2010[143]	NR	NR	R-DHAX all patients: Dose modification at baseline=22% Dose modification during treatment=23%	Grade 3-4 toxicity: Anaemia=9% Neutropenia=44% Thrombocytopenia=47%
	NR	NR	<60 Dose modification at baseline=9% Dose modification during treatment=21%	Grade 3-4 toxicity: Anaemia=5% Neutropenia=46% Thrombocytopenia=44%
	NR	NR	60-70 Dose modification at baseline=23% Dose modification during treatment=27%	Grade 3-4 toxicity: Anaemia=10% Neutropenia=33% Thrombocytopenia=49%
	NR	NR	>70 Dose modification at baseline=22% Dose modification during treatment=23%	Grade 3-4 toxicity: Anaemia=9% Neutropenia=44% Thrombocytopenia=47%

AST=aspartate transaminase; ALT=alanine transaminase; NHL=non-Hodgkin's lymphoma; RDI=relative dose intensity; PS=performance status; CEEP=cyclophosphamide, Epirubicin, Etoposide, Prednisolone; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; DA-REPOCH=dose adjusted eptoposide, vincristine, doxorubicin, cylophosphamide and prednisone, plus rituximab; R-DHAX=dexamethasone, cytarabine, oxilaplatin plus rituximab; R-CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone plus rituximab; NR=not reported

10.4 Geriatric assessment and quality of life

One study reported data relating to CGA. Toaka et al[137] used the ADL as a baseline measure, with repeat measures of the tool used throughout the study. Details are presented in Table 21.

Table 21 Geriatric assessment and quality of life, retrospective studies

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
Taoka 2010[137]	ADL	Used as a baseline measure and outcome measure	NR	NR

ADL=Activities of Daily Living; NR=not reported

10.5 Summary and discussion

Due to the heterogeneity and lack of methodological quality of the included retrospective studies, useful comparison across studies and outcomes was not possible. The data from retrospective studies are difficult to interpret in any meaningful way; however, the data have been included for completeness to show the extent of the evidence base and for reference.

It should be noted that although retrospective evidence is not ranked as highly as evidence derived from RCTs, many of the retrospective studies included patients who more closely reflect the patients seen in routine clinical practice.

11 DISCUSSION

The World Health Organisation[13] states that most countries of the developed world have accepted the chronological age of 65 years as a definition of 'elderly' or 'older', whereas the British Geriatrics Society[14] describes geriatric medicine as being mainly concerned with people aged over 75 years. As expected, one of the key findings of this review is that there is no commonly used definition to describe the age (or age range) of 'older' patients who are recruited to NHL studies. The age of patients described as 'older' varied greatly across the included studies.

The inclusion of 18 RCTs that enrolled only older patients represents a substantial body of evidence, and reflects the prevalence of NHL in the older population. However, due to the poor methodological quality (based on the use of standardised quality assessment tools) and the relatively small size of the included trials, it has not been possible to synthesise the data in any meaningful way. Despite their weaknesses, many of the included trials have helped to shape UK clinical practice, and it must be noted that conducting good-quality trials to treat a complex, heterogeneous disease can prove challenging.

Data from the included RCTs are not generalisable to the older population with NHL. Strict patient selection processes ensure that patients who are recruited to RCTs are generally fitter and healthier than patients seen in routine clinical practice. However, data may be generalisable to the subgroup of older patients with NHL seen in routine clinical practice who are generally fit and healthy.

Evidence from the included non-RCT studies was generally derived from methodologically poor-quality, small studies published in abstract format. The characteristics of the patient populations in the cohort and retrospective studies indicate that patients were slightly more frail than patients included in the RCTs. Evidence from the retrospective studies may be more generalisable to the older population with NHL in general, as patients included in these studies were not selected for fitness or comorbidity. However, some regimens used in the studies are now obsolete, and many studies included data collected in the 1990s. These factors, together with the heterogeneous nature of the studies, mean that any synthesis or comparisons are not possible or, indeed, warranted.

Efficacy outcomes were well reported; however, comparisons are difficult due to the variability in outcomes reported. Taking all of this into consideration, this review presents evidence which shows that, in general, chemotherapy can be effective in fit, older people with NHL; there are data to suggest that chemotherapy does confer survival benefit to older patients, and studies generally concluded that chemotherapy is a feasible treatment option for older people with NHL.

Although the majority of studies reported comprehensive data relating to tolerability, the data were difficult to interpret because of variations in the measures used and the outcomes reported. The

measurement of tolerability is often subjective in clinical practice, and therefore results are variable and not necessarily objective. There were some issues raised relating to the tolerability of treatment; clinical advisors suggest that in clinical practice for many older patients, well tolerated regimens are less likely to be effective. For aggressive NHL, the aim is to cure patients, and any reduction in QoL due to toxicity is returned to normal once treatment has finished.

The reporting of QoL was infrequent and inconsistent across all study types, making it difficult to draw conclusions for the older population. This review highlights the lack of QoL data in NHL clinical trials. The review also demonstrates that there are severely limited data relating to the use of CGA, either to guide decisions regarding the choice of treatment or as an outcome measure. Clinical advisors to the review suggest that CGA is not widely utilised in the context of clinical practice for the treatment of NHL in the UK due to a lack of resources, and this is perhaps reflected in the trials.

11.1 Strengths and limitations

One of the main strengths of this review is that a large volume of evidence from a wide range of studies has been collated to form a comprehensive evidence base describing how older patients with NHL are treated in clinical studies. However, the inclusion criteria employed in this review were deliberately broad and led to the inclusion of diverse studies: study populations were often very different in terms of disease stage and histology, treatment type and line of treatment across the studies. As there is considerable heterogeneity, it is not possible to draw firm conclusions for specific subgroups of older patients with NHL.

Overall, the quality of the included studies was poor and, therefore, the results must be viewed with caution. Many of the studies, particularly the RCTs, selected fitter, healthier patients and the results are not necessarily generalisable to the population of older people with NHL seen in routine clinical practice. There was great variability across the included studies in terms of which outcome measures were utilised and how these outcomes were reported; meaningful interpretation and comparison of efficacy, tolerability, QoL and CGA outcomes are therefore difficult.

Although the results of this review highlight that chemotherapy may be a viable treatment option for fit, older people with NHL, it should be noted that any conclusions drawn are not treatment recommendations; the evidence should instead be used to enable clinicians and patients to have discussions about treatment options.

12 CONCLUSIONS

There is much research into the treatment of 'older' or 'elderly' people with NHL, but it is generally of poor quality. There is a lack of consistency in NHL trials, such as the definition of 'older' or 'elderly', and the use and reporting of standard assessment measures for outcomes such as efficacy and tolerability. There are few data collected for QoL and CGA.

Chemotherapy can benefit fit, older patients, but there is a risk of increased toxicity for many regimens used to treat aggressive NHL. Older patients should therefore have an opportunity to discuss treatment options with healthcare professionals. Even though age is a risk factor for toxicity, age alone should not be a barrier to chemotherapy for patients with NHL, as other factors including fitness, comorbidities and personal choice should be taken into account.

12.1 Considerations for future research

A potential area in which to focus future research would be the management of older patients outside of the context of a clinical trial, for example the rationale for undergoing treatment, what treatments are used and why. The treatment of older patients with NHL is constantly under review, and future research should reflect this.

It is essential that any future clinical trials adopt more uniform definitions and standardised assessment tools that measure outcomes objectively, particularly in relation to tolerability and QoL. Outcomes should also be reported consistently to enable meaningful synthesis of data, so that each study adds valuable information to the evidence base.

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14 APPENDICES

Appendix 1: Literature search strategies

Elderly Cancer Search History (35 searches)
Ovid MEDLINE® and Ovid OLDMEDLINE® 1946 to Present with Daily Update

# ▲	Searches	Results
1	exp Breast Neoplasms/	206832
2	(breast$ adj5 (neoplasm$or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	57204
3	exp Colorectal Neoplasms/	139935
4	(colorectal adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	63395
5	exp Lung Neoplasms/	165165
6	(lung adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	116112
7	exp Carcinoma, Renal Cell/	20951
8	((renal cell or kidney) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	21641
9	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ or exp Leukemia, Myeloid, Chronic-Phase/ or exp Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative/	15723
10	(chronic myel$ adj2 leuk?emia).ti,ab.	19580
11	exp Lymphoma, Non-Hodgkin/	80985
12	(Lymphoma$ adj5 (non-hodgkin$ or non hodgkin$)).ti,ab.	28219
13	or/1-12	663599
14	*"Aged, 80 and over"/ or *Aged/	21737
15	(senil$ or geriatr$ or older or elder$ or late-life or later-life or late$ life).ti,ab.	392827
16	14 or 15	401572
17	13 and 16	15012
18	163hemotherapy$.tw. or drug therapy.fs.	1734499
19	(adjuvant adj5 chemotherap$).tw.	17651
20	exp Antineoplastic Agents/ or exp Antineoplastic Combined Chemotherapy Protocols/ or exp Chemotherapy, Adjuvant/	821443
21	or/18-20	2172920
22	exp Medication Adherence/ or adherence.tw.	58141
23	(survival adj benefit$).tw.	7695
24	(recurrence risk$ or relapse-free survival).tw.	6612
25	exp Drug Toxicity/ or exp Drug Tolerance/ or exp Safety/ or exp Treatment Outcome/ or exp Disease-Free Survival/	719437
26	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).tw.	208607
27	(side effect$ or undesirable effect$ or treatment-emergent or treatment-related or tolerability or safety or toxic effect$ or dose intensity or toxicity).tw.	617560
28	(clinical adj5 (effectiveness or efficacy or effect$ or benefit$)).tw.	113247
29	exp "Quality of Life"/ or (quality of life or qol).tw.	164254
30	or/22-29	1568681
31	21 and 30	520864
32	17 and 31	2926
33	(animals not (humans and animals)).sh.	3760147
34	32 not 33	2924
35	**limit 34 to (163hemoth language and yr="2000 -2013")**	2146

EMBASE Search History (33 searches)
Embase 1974 to 2013 May 24

# ▲	Searches	Results
1	exp breast cancer/	258454
2	(breast$ adj5 (neoplasm$or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	75564
3	exp colon carcinoma/ or exp colon cancer/ or exp colorectal cancer/ or exp rectum cancer/ or exp rectum carcinoma/	158617
4	(colorectal adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	89748
5	exp lung tumor/ or exp lung cancer/	241425
6	(lung adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	160685
7	exp kidney cancer/	65356
8	((renal or kidney) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	62964
9	exp chronic myeloid leukemia/	28802
10	(chronic myel$ adj2 leuk?emia).ti,ab.	24827
11	exp nonhodgkin lymphoma/	116117
12	(Lymphoma$ adj5 (non-hodgkin$ or non hodgkin$)).ti,ab.	37418
13	or/1-12	878499
14	exp geriatric patient/ or *aged/	50605
15	(senil$ or geriatr$ or older or elder$ or late-life or later-life or late$ life).ti,ab.	531929
16	14 or 15	546878
17	13 and 16	22973
18	164hemotherapy$.tw.	353300
19	(adjuvant adj5 chemotherap$).tw.	26741
20	exp antineoplastic agent/ or exp consolidation chemotherapy/ or exp multimodal chemotherapy/ or chemotherapy/ or exp induction chemotherapy/ or exp cancer combination chemotherapy/ or exp maintenance chemotherapy/ or exp cancer chemotherapy/ or exp adjuvant chemotherapy/ or exp combination chemotherapy/	1462883
21	or/18-20	1546201
22	(clinical adj5 (effectiveness or efficacy or effect$ or benefit$)).tw.	165108
23	*patient compliance/ or adherence.tw.	149576
24	(survival adj benefit$).tw.	12002
25	(recurrence risk$ or relapse-free survival).tw.	9402
26	exp drug toxicity/ or exp drug tolerance/ or exp drug safety/ or exp treatment outcome/ or exp disease free survival/	1218587
27	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).tw.	311356
28	(side effect$ or undesirable effect$ or treatment-emergent or treatment-related or tolerability or safety or toxic effect$ or dose intensity or toxicity).tw.	886887
29	exp “quality of life”/ or (quality of life or qol).tw.	277356
30	or/22-29	2407159
31	21 and 30	418422
32	17 and 31	5575
33	**limit 32 to (human and 164hemoth language and yr=”2000 – 2013”)**	**4047**

The Cochrane Library, Issue 2 of 4, April 2013
Search History

[Breast Neoplasms] explode all trees 7763
breast cancer* or breast neoplasm* or breast tumour* or breast carcinoma*:ti,ab,kw (Word variations have been searched) 14703
[Colorectal Neoplasms] explode all trees 4628
"colorectal cancer":ti,ab,kw (Word variations have been searched) 4311
[Lung Neoplasms] explode all trees 4272
"lung cancer":ti,ab,kw (Word variations have been searched) 6836
[Carcinoma, Renal Cell] explode all trees 419
kidney cancer or renal cell cancer:ti,ab,kw (Word variations have been searched) 789
[Leukemia, Myelogenous, Chronic, BCR-ABL Positive] explode all trees 304
"chronic myeloid leukaemia":ti,ab,kw (Word variations have been searched) 101
[Lymphoma, Non-Hodgkin] explode all trees 1136
non-hodgkin's lymphoma:ti,ab,kw (Word variations have been searched) 1203
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 30561
(senil* or geriatr* or older or elder* or late-life or later-life or late*):ti,ab,kw (Word variations have been searched) 67255
Aged] explode all trees 554
#14 or #15 67394
#13 and #16 2332
(165hemotherapy* or drug therap*):ti,ab,kw (Word variations have been searched) 111982
MeSH descriptor: [Drug Therapy] explode all trees 108765
#18 or #19 173119
#17 and #20 1068

Web of Knowledge

Results:
Topic=(breast cancer* or colorectal cancer* or renal cell carcinoma* or chronic myeloid leukemia* or non-hodgkin lymphoma*) AND Topic=(165hemotherapy* or Bevacizumab or Avastin or Cetuximab or Erbitux or Everolimus or Afinitor or Fulvestrant or Faslodex or Lapatinib or Tyverb or Bendamustine or Levact or Bortezomib or Velcade or Rituximab or Mabthera or Rituxan) AND Topic=(aged or senil* or geriatr* or older or elder*)

Refined by: Languages=(ENGLISH) AND Web of Science Categories=(ONCOLOGY OR HEMATOLOGY) AND Document Types=(PROCEEDINGS PAPER OR MEETING ABSTRACT) AND Research Areas=(ONCOLOGY OR HEMATOLOGY)

Timespan=2000-01-01 – 2013-02-03. Databases=Conference Proceedings Citation Index- Science (CPCI-S).

Appendix 2: Quality assessment

The quality of RCTs was assessed using criteria based on CRD guidance.

- Was the method used to assign participants to the treatment groups really random?*
- Was the allocation of treatment concealed?**
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for withdrawals stated?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Was an intention-to-treat analysis included?
- Was the study sufficiently powered for the primary outcome(s)?

**(Computer-generated random numbers and random number tables were accepted as adequate, while inadequate approaches included the use of alternation, case record numbers, birth dates and days of the week)*

*** (Concealment was deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches included: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).*

Items were graded in terms of ✓ yes (item properly addressed), ✕ no (item not properly addressed), ✓/✕ partially (item partially addressed), **?** Unclear/not enough information, or **NA** not applicable

Appendix 3: Excluded studies

Study	Reason for exclusion	Study	Reason for exclusion
Abramson 2011[147]	No data	Cheson 2009[148]	Study type
Abrey 2000[149]	Treatment	Chimienti 2009[150]	Outcomes
Ahlgrimm 2011[151]	Outcomes	Choi 2009[152]	Population
Ahlgrimm 2009[153]	Outcomes	Choquet 2011[154]	No data
AlEjielat 2012[155]	No data	Coiffier 2002[156]	Discussion
Alimohamed 2012[157]	Treatment	Coiffier 2002[158]	Outcomes
Anderson 2006[159]	No data	Coiffier 2002[160]	Outcomes
Andrade 2012[161]	No data	Coiffier 2002[162]	Outcomes
Aoki 2011[163]	Outcomes	Coiffier 2003[164]	Discussion
Ardeshna 2003[165]	No data	Coiffier 2004[166]	Outcomes
Armitage 2002[167]	Study type	Copie-Bergman 2009[168]	No data
Armitage 2002[169]	Study type	Corazzelli 2010[170]	No data
Aviles 2007[171]	No data	Corazelli 2006[172]	Unavailable
Aviles 2010[173]	No data	Costa 2012[174]	Outcomes
Bairey 2013[175]	No data	Cronin-Fenton 2006[176]	No data
Bairey 2006[177]	Treatment	Cuttner 2002[178]	No data
Balducci 2002[179]	Study type	D'Amore 2012[180]	Population
Balducci 2012[179]	No data	De Sanctis 2004[181]	Population
Balducci 2004[182]	No data	DeAngelis 2001[183]	Outcomes
Baumgarten 2012[184]	Outcomes	Dell'Olio 2011[185]	Population
Ben Simon 2006[186]	No data	Delwail 2000[187]	Unavailable
Bennett 2010[188]	Outcomes	Dillman 2007[189]	No data
Bernardi 2004[190]	Outcomes	Dillman 2007[191]	No data
Bernardi 2005[192]	Outcomes	Doolittle 2010[193]	Population
Bertini 2001[194]	Study type	El Helw 2000[195]	Unavailable
Bessell 2004[196]	Treatment	Emmanouilides 2007[197]	Treatment
Bessell 2001[198]	Treatment	Errante 2008[199]	No data
Biagi 2005[200]	Population	Evens 2010[201]	Treatment
Bjorkholm 2007[202]	Treatment	Fantini 2011[203]	No data
Boehme 2009[204]	No data	Febbri 2011[205]	Discussion
Boehme 2007[206]	Outcomes	Ferreri 2012[207]	Outcomes
Boehme 2007[208]	No data	Fields 2012[209]	Discussion
Bordonaro 2004[210]	Study type	Fisher 2003[229]	Discussion
Bordanoro 2004[211]	No data	Flinn 2011[231]	Population
Bosley 2001[212]	Population	Flinn 2012[233]	Population
Burton 2006[213]	Outcomes	Flinn 2012[235]	Population
Busse 2007[214]	Population	Forconi 2008[237]	Population
Byrd 2012[215]	Population	Frata 2005[239]	Treatment
Caimi 2010[216]	Outcomes	Fratino 2004[241]	Treatment
Calderoni 2002[217]	No data	Fridrik 2010[243]	Treatment
Camara-Clayette 2012[218]	Study type	Ganti 2006[245]	Outcomes
Carson 2012[219]	No data	Gonzalez 2010[247]	No data

Goy 2012[249]	Population	Kluin-Nelemans 2011[250]	No data
Grann 2006[251]	Population	Knauf 2012[252]	No data
Green 2006[253]	Treatment	Knauf 2010[254]	No data
Griffiths 2010[255]	Treatment	Knight 2004[256]	Study type
Griffiths 2012[257]	Treatment	Knupp 2008[258]	Outcomes
Grigg 2003[259]	Treatment	Kouroukis 2002[260]	Study type
Gundrum 2009[261]	Treatment	Kouroukis 2001[262]	Discussion
Guo 2012[263]	Population	Kouroukis 2004[264]	Outcomes
Guo 2012[265]	Population	Kraeber-Bodere 2010[266]	Population
Gutierrez 2011[267]	No data	Krishnan 2005[268]	Treatment
Guyot 2010[269]	Population	Laack 2006[270]	Treatment
Hainsworth 2005[271]	No data	Latta 2013[272]	Study type
Haioun 2011[273]	No data	Lee 2012[274]	Population
Hajder 2012[275]	No data	Leitch 2003[276]	Treatment
Hamlin 2010[277]	No data	Lenz 2005[278]	No data
Heintel 2010[279]	No data	Leo 2004[280]	No data
Held 2006[281]	Study type	Lin 2010[282]	No data
Held 2006[283]	Treatment	Linch 2000[284]	No data
Helwick 2013[285]	Population	Link 2012[286]	Treatment
Henk 2011[287]	No data	Link 2013[288]	Outcomes
Hershman 2008[289]	Outcomes	Link 2011[290]	Treatment
Hershman 2008[291]	Outcomes	Lopez 2008[292]	No data
Hoelzer 2012[293]	Treatment	Lote 2000[294]	No data
Hosing 2007[295]	Treatment	Love 2010[296]	Population
Hosing 2008[297]	Treatment	Lowry 2013[298]	No data
Hosing 2006[220]	Population	Lu 2012[299]	Treatment
Huntington 2010[221]	Treatment	Lugtenburg 2008[301]	Discussion
Huntington 2012[222]	Population	Luptakova 2010[303]	No data
Intermesoli 2012[223]	No data	Lyman 2004[305]	No data
Inwards 2012[224]	Treatment	Lyman 2003[307]	No data
Inwards 2008[225]	No data	Maartense 2003[309]	Study type
Isogai 2007[226]		Maartense 2002[311]	Treatment
Ivanov 2012[227]	No data	Magagnoli 2010[313]	No data
Jantunen 2000[228]	Treatment	Magagnoli 2003[315]	Treatment
Jonak 2010[230]	Population	Manolopoulos 2009[317]	No data
Jung 2011[232]	No data	Marcus 2003[319]	No data
Kalaycio 2006[234]	Treatment	Martin 2012[321]	No data
Kalpadakis 2007[236]	No data	Martinelli 2003[323]	No data
Keating 2010[238]	No data	Mazzola 2006[325]	Population
Kelly 2012[240]	No data	Mead 2000[327]	No data
Kelly 2009[242]	Treatment	Melchardt 2012[329]	Population
Kenkre 2011[244]	No data	Meyer 1995[331]	Population
Kim 2010[246]	No data	Mian 2011[333]	Treatment
Kiserud 2009[248]	No data	Mileshkin 2005[335]	Population

Miyazaki 2011[337]	Population	Quaglino 2011[338]	No data
Montillo 2010[339]	No data	Rao 2007[340]	No data
Morrison 2007[341]	Population	Rasmussen 2009[342]	Treatment
Morrison 2008[343]	Study type	Ribera 2011[344]	Population
Morrison 2001[345]	Study type	Ribrag 2012[346]	No data
Morschhauser 2009[347]	No data	Rigacci 2004[348]	Population
Musolino 2011[349]	Outcomes	Rodriguez 2007[350]	No data
Nabhan 2010[351]	No data	Rossini 2004[352]	No data
Nastoupil 2012[353]	Study type	Rummel 2012[354]	No data
Ney 2010[355]	Treatment	Sabloff 2004[356]	Population
Ninan 2009[357]	Study type	Salles 2010[358]	No data
Nishikii 2011[359]	No data	Salvagno 2002[360]	Population
Nowakowski 2012[361]	No data	Sawada 2002[362]	No data
Oerlemans 2011[363]	No data	Schmits 2005[364]	Population
Osby 2004[365]	Outcomes	Schmitz 2008[366]	Outcomes
Osby 2002[367]	Outcomes	Scholz 2013[368]	No data
Osby 2003[369]	Population	Schubert 2006[370]	Population
Pallardy 2011[371]	No data	Schuurmans 2010[372]	Population
Pan 2010[373]	Population	Sehl 2007[374]	Outcomes
Parcelier 2012[375]	No data	Shen 2012[376]	Population
Pectasides 2000[377]	No data	Shikama 2006[378]	Treatment
Pels 2006[379]	Population	Shikama 2011[380]	Treatment
Pennese 2009[381]	No data	Siegel 2007[382]	Outcomes
Perepu 2012[383]	Population	Smith 2012[384]	Outcomes
Pettengell 2011[385]	Population	Smolej 2011[386]	No data
Pfreundschuh 2010[300]	Outcomes	Smolej 2010[387]	Population
Pfreundschuh 2011[302]	Population	Sonneveld 2006[388]	Outcomes
Pfreundschuh 2011[304]	Population	Sonneveld 2005[389]	Outcomes
Pfreundschuh 2005[306]	Population	Soubeyran 2011[390]	No data
Pfreundschuh 2006[308]	Population	Stefoni 2005[391]	Outcomes
Pfreundschuh 2009[310]	Population	Takahashi 2012[392]	Population
Pfreundschuh 2008[312]	Population	Taylor 2006[393]	No data
Pfreundschuh 2004[314]	Population	Thieblemont 2007[394]	Study type
Pfreundschuh 2007[316]	Treatment	Thieblemont 2008[395]	Treatment
Pfreundschuh 2008[318]	Treatment	Thomas 2006[396]	No data
Plosker 2003[320]	No data	Tirelli 2002[397]	Population
Poeschel 2006[322]	Outcomes	Tirelli 2001[398]	Study type
Portlock 2002[324]	Ni data	Tirelli 2011[399]	No data
Poschel 2008[326]	No data	Tiwari 2008[400]	Population
Pott 2010[328]	Population	Tokunaga 2012[401]	Population
Prabhakar 2011[330]	No data	Toomey 2010[402]	Population
Pregno 2003[332]	No data	Tsang 2001[403]	Discussion
Purroy 2011[334]	No data	Veneri 2002[404]	No data
Qian 2006[336]	Outcomes	Visani 2009[405]	Study type

Visco 2011[406]	No data
Vitolo 2010[407]	No data
Voelker 2004[408]	Outcomes
Wang 2011[409]	Treatment
Weide 2008[410]	Population
Wenger 2005[411]	No data
Wohrer 2003[412]	No data
Wohrer 2005[413]	No data
Wunderlich 2003[414]	Treatment
Zhai 2010[415]	Population
Zhu 2011[416]	Population
Ziepert 2010[417]	Study type
Zinzani 2003[418]	Study type
Zinzani 2010[419]	No data
Zinzani 2008[420]	No data
Zinzani 2004[421]	No data
Zouhair 2002[422]	Treatment
Zwick 2007[423]	Population
Zwick 2009[424]	Study type
Zwick 2011[425]	Population

Appendix 4: Comprehensive geriatric assessment, all study types

Study	Results
RCTs	
Merli 2012[19]	IADL 99 patients were considered as 'unfit' at CGA and were not randomised
Comparative cohort	
Vitolo 2011[51]	Unspecified CGA According to CGA, concomitant illness were: one in 38% and ≥2 in 23% of patients
Single cohorts	
Tucci 2009[75]	ADL, CIRS-G According to CGA, 42 of 84 (50%) patients were classified as fit and 42 (50%) as unfit. The criteria for classifying a patient as unfit were age in 15 (35.7%), low ADL in 4 (11.9%), comorbidity in 20 (50%), and geriatric syndrome in 3 cases (7.1%), respectively. All the patients with geriatric syndrome had further concomitant reasons for being considered unfit (low ADL score in 1, comorbidity in 1, both low ADL and comorbidity in 1). The 2 subgroups of fit and unfit patients differed significantly in mean age (70.8 years vs 76.3 years; p<.0001)
Spina 2012[58]	ADL, IADL, Geriatric depression, MMS (mini mental state), CIRS-G Based on the results of the modified CGA, patients were stratified into three groups. The 'fit' group included patients with no grade 3 comorbidities (or <3 grade 2 comorbidities), an ADL score of 6, and/or an IADL score of 7 or 8. The 'unfit' group included patients with no grade 3 comorbidities (or 3-5 grade 2 comorbidities), an ADL score of 5, and/or an IADL score of 5 or 6. The 'frail' group included patients with one or more grade 3 comorbidities (or more than five grade 2 comorbidities), an ADL score <5, or an IADL score <5
Retrospective studies	
Taoka 2010[137]	ADL ADL improvement was evaluated using the baseline index. In all patients, the ADL improved and was maintained after the induction chemotherapy; the median baseline index scores before and after the induction therapy were 45 and 95, respectively. Unless they had lymphoma progression, no patients showed any decrease in baseline index scores throughout the period of maintenance therapy

ADL=Activities of Daily Living; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; CGA=comprehensive geriatric assessment; IADL=Instrumental Activities of Daily Living; MMS=mini-mental status

Appendix 5: Quality of life, all study types

Study	Tool used	Results	Compliance
RCT			
Merli 2007[23]	EORTC QLQ-C30 questionnaire	Baseline QoL assessment showed a strong correlation of poor values of QoL with anaemia and high risk according to the IPI. At the end of treatment no functional scales showed worse values. A significant improvement was observed for pain (p=0.003), appetite (p=0.006), sleep (p=0.015), and global health (p=0.027). Considering only the 50 patients who achieved a CR, an improvement was also recorded for emotional state (p=0.10), role (p=0.05), constipation (p=0.04), and global QoL (p=0.05). No significant differences in terms of QoL changes were found between patients treated with P-VEBEC and those treated with Mini-CEOP	QoL was investigated in 156/232 patients (67%), although only 91 patients completed both pretherapy and post-therapy questionnaires
Doorduijn 2003[28]	EORTC QLQ-C30 questionnaire	They differed from the total study population only by the higher frequency of B symptoms (36% vs 26%). During the study period, 96% of the questionnaires were returned, and in the follow-up period, 88% were returned. In patients with progressive disease or relapse, the questionnaire return rate decreased to 77%. As there was no difference in QoL between the two treatments, the results are combined. During treatment, the EuroQol did not change. The mean QLQ-C30 scores for the different domains did not change in time. Patients with B symptoms scored significantly lower before treatment on almost all scales. This difference was no longer present after four chemotherapy cycles. There was an inverse association between fatigue and haemoglobin level at all time points. During follow-up, the QoL scores were attributed to the different clinical outcomes: CR, PR, or progression or relapse. Three months after completion of therapy, patients with PR or CR reported significantly higher levels of QoL compared with pretreatment and during-treatment values. Only the patients with progression or relapse reported a significantly lower QoL. With longer follow-up, no major changes occurred in QoL	162 patients were asked to participate in the QoL study. 30 refused (19%)

CR=complete response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life cancer questionnaire; IPI=International Prognostic Index; Mini-CEOP=cyclophosphamide, epidoxorubicin, vinblastine and prednisone; PR=?????; P-VEBEC=Epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin and prednisone; QoL=quality of life