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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Systematic review to examine the clinical effectiveness and tolerability of chemotherapy treatment for older people with breast cancer

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Title:
Systematic review to examine the clinical effectiveness and tolerability of chemotherapy treatment for older people with breast cancer

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Abbreviations:

AC	Doxorubicin plus cyclophosphamide
AC-T	Doxorubicin, cyclophosphamide and paclitaxel
ADL	Activities of Daily Living
AE	Adverse event
BMI	Body mass index
CAF	Cyclophosphamide, doxorubicin and fluorouracil
CALGB	Cancer and Leukemia Group B
CCI	Charlson Comorbidity Index
CEF	Cyclophosphamide, epirubicin and 5-fluorouracil
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CM	Metronomic cyclophosphamide and methotrexate
CMF	Cyclophosphamide, methotrexate and 5-fluorouracil
DFS	Disease-free survival
E-CMF	Epirubicin plus CMF
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-BR23	EORTC quality of life breast cancer specific questionnaire
EORTC-QLQ-C30	EORTC quality of life cancer questionnaire
FACT-B	Functional Assessment of Cancer Therapy-Breast
FEC-100	5-fluorouracil, epirubicin and cyclophosphamide
GDS	Geriatric Depression Scale
HER2	Epidermal growth factor receptor 2
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
HRQoL	Health-related quality of life
IADL	Instrumental Activities of Daily Living
IPD	Individual patient data
ITT	Intention to treat
KPS	Karnofsky performance status
LASA	Linear Analogue Self-Assessment
MGA	Multidimensional Geriatric Assessment
MMM	Methotrexate, mitoxanthrone and mitomycin C
MMS	Mini-mental status
NCEI	The National Cancer Equality Initiative
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PLD	Pegylated liposomal doxorubicin
POI	Pharmaceutical Oncology Initiative
PS	Performance status
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity

SD	Standard deviation
SE	Standard error
TAC	Docetaxel, doxorubicin and cyclophosphamide
TC	Docetaxel plus cyclophosphamide
TTP	Time to disease progression
VES	Vulnerable Elders Survey

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 anti-cancer 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
Oestrogen receptor-negative (ER-)	Cancer cells that are oestrogen receptor negative do not need oestrogen to grow
Oestrogen receptor-positive (ER+)	Cancer cells that may need oestrogen to grow (and can thus be treated with anti-oestrogen therapy)

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 Equality 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 consider the evidence for the clinical effectiveness and tolerability of chemotherapy regimens used to treat breast cancer 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 at stage 2 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 (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.

Evidence synthesis

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

1.4 Results

Electronic searching of databases resulted in 5716 references. Manual de-duplication of references resulted in 5548 unique references for screening at stage 1. Initial screening identified 147 references, which were obtained as full-text papers. A total of 74 studies (reported in 91 references) met the inclusion criteria at stage 2 and were included in the review. Studies were divided into six categories, based on study design.

The review included data from eight RCTs, five subgroups of RCTs, seven pooled analyses, 34 single or comparative cohort studies, and 20 retrospective studies.

1.5 Conclusions

This review presents evidence which shows that chemotherapy does confer some survival benefit to older patients, and studies generally conclude that chemotherapy is a feasible treatment option for older people with breast cancer.

The data suggest that older people can tolerate chemotherapy, although treatment comes with a risk of more serious adverse events.

The results from older patients are generally similar to those from younger patients, which suggests that age should not be a barrier to treatment for breast cancer, and that older age should not disqualify people from being eligible for clinical trials.

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

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 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 fully assessed when treating older people with cancer, some of whom may be able to tolerate effective treatment.

The National Cancer Equality 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.

Older patients are underrepresented in clinical trials, and those who are included do not generally represent the older population as 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

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue affecting predominantly women, and is the most common cancer affecting women in the UK. Though frequently referred to as a homogeneous disease, breast cancer has been recognised as a biologically heterogeneous disease with several subgroups including those with different stages and types of the disease.[1] In the period 2008-2010, 90% of female breast cancer deaths in the UK were in women aged over 50, with age-specific mortality rates in the UK peaking at age 85 and over.[2]

2.1.1 Aetiology

After gender, the strongest risk factor for breast cancer is age; the incidence of breast cancer increases with age. In the UK between 2008-2012, 80% of all diagnoses were in those aged ≥50 years, and 45% were diagnosed in women aged ≥65 years.[3] Female breast cancer incidence rates have increased in the UK over the past 30 years. Over time, the largest increases in UK incidence rates have been in women aged 65 to 69 and 50 to 64 years.

2.1.2 Pathology and prognosis

Several prognostic factors are considered by clinicians when deciding on treatment options and making a clinical prognosis,[4] including age, tumour size, histological type and grade, nuclear grade, number of metastatic axillary lymph nodes and clinical stage.

For the period 2005-2009 in England, the 5-year relative survival rates for breast cancer were 84% in those aged 15 to 39 years, 90% in those aged 50 to 69 years, and 69% in those aged 80 to 99 years.[5]

2.1.3 Current treatment options

There are differences in treatment options for early breast cancer and advanced or metastatic breast cancer.

Early breast cancer

The aims of treatment for early breast cancer are to eradicate the cancer and minimise the risk of disease recurrence, with as few side-effects and risks to the patient as possible. For the majority of patients, initial treatment is with surgery to the breast and axillary lymph nodes. After surgical removal of the primary cancer, adjuvant treatment may be offered to reduce the risks of disease recurrence over the forthcoming years. For early breast cancer this may involve radiotherapy, chemotherapy, biological therapy or anti-oestrogen therapy.

Advanced or metastatic breast cancer

Metastatic breast cancer is incurable; the median survival of patients with metastatic breast cancer is 2 to 3 years. The aims of treatment are the prolongation of survival and maintenance of best possible quality of life. Treatment may include endocrine therapy, cytotoxic chemotherapy, biological agents and supportive approaches such as palliative radiotherapy and bone therapy.

3 AIMS AND OBJECTIVES

3.1 Objectives

The aim of this review is to systematically consider the evidence for the clinical effectiveness and tolerability of chemotherapy regimens used to treat breast cancer 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 related 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 breast cancer. There is no agreed definition of 'older'; The World Health Organisation[6] 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[7] 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.

All forms of chemotherapy (defined as a systemic anti-cancer therapy) 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 effective in clinical practice. Moreover, targeted therapies such as bevacizumab and lapatinib are frequently considered by the Cancer Drugs Fund.[8] Hormonal therapies have not been included in this review as they are not considered to be chemotherapy or equivalent to chemotherapy.

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 Table 1. 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 breast cancer
Interventions	Any chemotherapy (all lines of treatment)
Comparators	• an alternative chemotherapy or • best supportive care
Outcomes	Efficacy outcomes: • overall survival • progression-free survival • response rates Tolerability outcomes: • adverse events • tolerability Other outcomes: • Quality of life (QoL) • Comprehensive geriatric assessment (CGA)
Other considerations	Papers that reported subgroup analyses for older people in their abstract were included Only studies published since 2000 in full or with an English language abstract were included

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 for 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.

Comprehensive 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 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.

Included RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance.[9] 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 the quality assessment criteria used are provided in Appendix 2.

No universally accepted standardised quality assessment tool exists for use in observational studies. There are a multitude of observational 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 observational 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 observational 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 5716 references. Manual de-duplication of references resulted in 5548 unique references available for screening at stage 1. See Figure 1 for details.

Initial screening identified 147 references, which were obtained as full-text papers. A total of 74 studies (reported in 91 references) met the inclusion criteria at stage 2 and were included in the review. A list of references excluded at stage 2 is presented in Appendix 3. The 74 studies included in the review were divided into six 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
Randomised controlled trials (RCTs)	RCTs recruiting only patients defined as elderly/older	8
Subgroup analyses of RCTs	Analyses of RCTs from the general population with elderly/older subgroups reported separately	5
Pooled analyses	Published studies that use aggregated subgroup data on elderly/older patients from RCTs or cohort studies	7
Comparative cohorts	Studies which report two or more comparators of a non-randomised trial with an elderly/older population	3
Single cohorts	Studies which report single cohorts of elderly/older patients	31
Retrospective data	Any reports of chemotherapy treatment for elderly/older patients in a defined cohort of patients or as report from registries of patient outcomes	20
Total		**74**

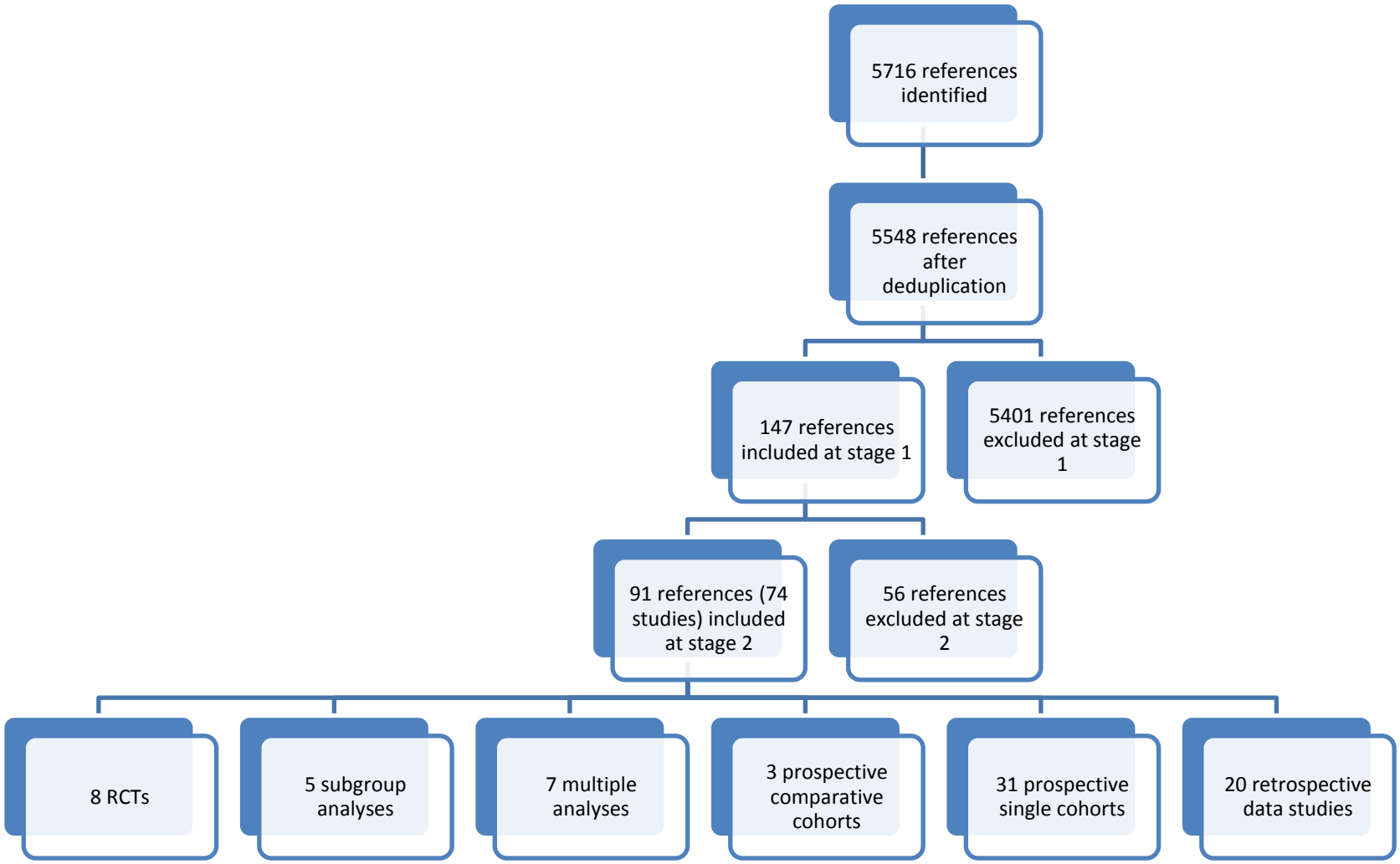


Figure 1 Flow diagram of included studies

6 RANDOMISED CONTROLLED TRIALS

A total of eight RCTs were included in the review (reported in 14 publications).[10-23] Where one RCT is reported in multiple publications, only the key paper or most recent publication is included in the summary. Both Seynaeve et al[23] and Latorre et al[15] were available as abstracts only.

6.1 Quality assessment

Full details of the quality assessment criteria used are presented in Appendix 2. Results of the quality assessment of included RCTs are shown in Table 3. The abstracts published by Latorre et al[15] and Seynaeve et al[23] did not provide sufficient methodological information to be included in the quality assessment exercise.

Three of the included RCTs were assessed as adequately randomised[17,19,21] however, none of the trials reported sufficient information to be considered as having adequate concealment of allocation.

All RCTs clearly reported the number of participants randomised. Baseline characteristics were presented in all trials, and with the exception of Romieu et al[21] all trials achieved baseline comparability.

Only one trial[19] reported that assessors were blinded to treatment allocation, although patients and administrators in this trial were not blinded.

All trials reported reasons for withdrawals and included >80% of participants in the final analysis. An intention to treat (ITT) analysis was undertaken in three trials[16,17,19] and three trials were sufficiently powered to measure primary outcomes.[10,16,19]

6.2 Study characteristics

6.2.1 Overview

Trial and patient characteristics are presented in Table 4, which details information on patients with early breast cancer and those with advanced or metastatic disease, respectively. Where possible, data regarding age and performance status (PS) are presented in detailed breakdowns; however, not all trials presented key information and therefore there are some missing data.

Overall, there were five phase III trials[10,12,15-17] and two phase II trials.[19,21] Seynaeve et al[23] did not specify the phase. Four trials[10,12,19,21] were international and five were multicentre.[12,17,19,21,23] Five trials were funded by pharmaceutical companies;[10,12,16,19,21] Latorre et al[15] and Seynaeve et al[23] did not provide any funding information. The trials ran between 1996 and 2007; the smallest trial was Latorre et al,[15] which randomised a total of 37 patients, and the largest trial, Muss et al[16] randomised 633 patients.

The median age of patients across trials ranged from 67.5 to 75 years, and the definition of older ranged from >55 to >70 years of age. The PS was similar across all trials, with the majority of patients being Eastern Cooperative Oncology Group (ECOG) 0-1 or the Karnofsky performance status (KPS) equivalent of >80.

6.2.2 Early breast cancer

Four trials focussed on patients with early breast cancer[10,16,17,21] and were conducted between 2001 and 2007. With the exception of Nuzzo et al[17] and Muss et al,[16] the trials were relatively small and randomised fewer than 100 patients. With the exception of Muss et al,[16] which was conducted in the USA, trials were conducted in European countries. All trials focussed on adjuvant chemotherapy.

The median age range of patients was narrow. Romieu et al[21] had the lowest median age of 67.5 years and Crivellari et al[10] had the highest at 75 years. The PS was similar across trials, with the majority of patients scoring 0 using ECOG criteria. Muss et al[16] reported that at least 96% of patients were ECOG 0-1 in both arms.

Table 4 presents the conclusions of the study authors, as published. The conclusions suggest that adjuvant chemotherapy for older people with early breast cancer is a feasible treatment option.

6.2.3 Advanced or metastatic breast cancer

Four trials focussed on patients with metastatic disease.[12,15,19,23] Most trials were small – only Feher et al[12] randomised more than 100 patients. Unfortunately, only two[12,19] of the trials were reported in full. Median age varied from 68 to 75 years. The PS of the majority of patients across trials was KPS 90-100; Seynaeve et al[23] reported 77% of patients were ECOG 0-1.

The authors' conclusions suggest that chemotherapy was well tolerated by older patients, and is a feasible treatment option.

Table 3 Quality assessment, randomised controlled trials

Study	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		Other measures	Intention to treat	Powering
	Truly random	Allocation concealment	Number stated	Baseline presented	Baseline achieved			Assessors	Administrators	Participants	Procedure assessed	>80% in final analysis	Reasons stated			
O'Shaughnessy 2001[19]	✓	?	✓	✓	✓	✓	×	✓	×	×	NA	✓	✓	×	✓	✓
Feher 2005[12]	?	×	✓	✓	✓	✓	×	×	×	×	NA	✓	✓	×	×	×
Romieu 2007[21]	✓	×	✓	✓	×	✓	×	NA	NA	NA	NA	✓	✓	×	×	×
Nuzzo 2008[17]	✓	×	✓	✓	✓	✓	×	×	×	×	×	✓	✓	×	✓	×
Muss 2009[16]	?	×	✓	✓	✓	✓	×	×	NA	NA	NA	✓	✓	×	✓	✓
Crivellari 2013[10]	?	×	✓	✓	✓	✓	✓	×	×	×	NA	✓	✓	✓/×	×	✓

Items are 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

Table 4 Study characteristics, randomised controlled trials

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Study conclusions
Early breast cancer						
Romieu 2007[21]	Phase II Multicentre International 14 centres in France, Germany, Spain, UK, Switzerland 2002-2004 Follow-up 30 days post-treatment Amgen	Adjuvant chemotherapy Node positive stage II-III Chemotherapy naïve Aged ≥65 years	FEC-100 with pegfilgrastim (n=31)	Median age: 67.5 years (65-77) ECOG PS: 0=28 (90%) 1=2 (6%)	Primary: Prevention of grade 3-4 neutropenia and fever Secondary: Tolerability, incidence of hospitalisation due to febrile neutropenia	These data indicate that delivery of FEC-100 is feasible with pegfilgrastim support in elderly breast cancer patients
			FEC-100 with pegfilgrastim if neutropenic event (n=29)	Median age: 69 years (65-75) ECOG PS: 0=24 (83%) 1=5 (17%)		
Nuzzo 2008[17]	Phase III Multicentre Italy 2003-2006 Clinical Trials Unit of the National Cancer Institute of Naples	Adjuvant chemotherapy Early breast cancer, with average or high risk of recurrence Aged 65–79 years	CMF (n=53)	Median age: 69 years (65-80) ECOG PS: 0=79.2% 1=20.8%	Primary: Disease-free survival (results due for collection June 2013) Secondary: Toxicity, compliance, QoL, OS	Weekly docetaxel appears to be less toxic than CMF in terms of haematological toxicity
			Docetaxel (n=48)	Median age: 70.5 years (65-79) ECOG PS: 0=81.3% 1=18.8%		
Muss 2009[16]	Phase III USA 2001-2006 Median follow-up 2.4 years National Cancer Institute, National Institute on Aging and Roche Biomedical Laboratories	Adjuvant chemotherapy Early stage breast cancer Aged 65 years and older	CMF (n=133) or AC (n=193)	Mean age: 72 years (SD 4.6) NCI PS: 0-1=97%	Primary: Relapse-free survival Secondary: OS, adverse events, adherence to oral chemotherapy, QoL and functional status	Standard adjuvant chemotherapy is superior to capecitabine in patients with early-stage breast cancer who are 65 years of age or older
			Capecitabine (n=307)	Mean age: 72 years (SD 5.0) NCI PS: 0-1=96%		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Study conclusions
Crivellari 2013[10]	Phase III International Italy, Hungary, Belgium, Australia, 2005- 2007 Median follow-up 42 months Partial support from Schering-Plough Company – funding withdrawn due to lack of accrual	Adjuvant chemotherapy Operable and endocrine non-responsive Aged >66 years	PLD (n=38)	Median age: 74 years (67-83) ECOG PS: 0=27 (75%) 1=7 (19%) 2=2 (6%)	Primary: Breast cancer-free interval Secondary: Tolerability (treatment completion), AEs and QoL	Based on our limited experience, PLD and CM may be reasonable options for further study for elderly vulnerable patients with endocrine non-responsive breast cancer
			Non-PLD (n=39)	Median age: 75 years (65-84) ECOG PS: 0=29 (76%) 1=9 (24%) 2=0 (0%)		
Advanced or metastatic breast cancer						
O'Shaughnessy 2001[19]	Phase II Multicentre International 23 centres in USA, Canada, Europe and Australia 1996-1997 F. Hoffmann-La Roche Ltd	First-line chemotherapy Locally recurrent or metastatic disease Chemotherapy naive Aged >55 years	Capecitabine (n=62)	Median age: 69 years (54-83) Median KPS 90	Primary: ORR Secondary: Safety, tolerability, OS, TTP, duration of response	An oral, twice-daily regimen of capecitabine is effective and well tolerated when used as first-line chemotherapy in older patients (≥55 years) with advanced/metastatic breast cancer, and is suitable for outpatient therapy
			CMF (n=33)	Median age: 70 years (55-80) Median KPS: 90		
Feher 2005[12]	Phase III International Multicentre 17 countries 1996-1999 Eli Lilly and Company	First-line chemotherapy Metastatic disease Aged ≥60 years	Gemcitabine (n=198)	Median age: 69 years (59-91) KPS: 60=16 (8.1%) 70=23 (11.7%) 80=51 (25.9%) 90=69 (35%) 100=35 (17.8%)	Primary: TTP Secondary: RR, duration of response, survival time, QoL, toxicity	Postmenopausal women >60 years of age with MBC tolerate chemotherapy well. In this study, epirubicin was superior to gemcitabine in the treatment of MBC in women age >60, confirming that anthracyclines remain important drugs for first-line

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Study conclusions
			Epirubicin (n=199)	Median age: 68 years (60-85) KPS: 60=10 (5.1%) 70=31 (15.7%) 80=44 (22.2%) 90=69 (35%) 100=40 (20.2%)		treatment of MBC
Latorre 2006 (abstract only)[15]	Phase III Italy	First-line chemotherapy Advanced metastatic breast cancer Chemotherapy naive Aged >70 years	Gemcitabine plus vinorelbine (n=19)	NR	OS, TTP, ORR and tolerability	In conclusion, these two combinations proved to be well tolerated and effective in elderly patients
			Gemcitabine plus mitoxantrone (n=18)			
Seynaeve 2012 (abstract only)[23]	Multicentre The Netherlands Follow-up 24 weeks	First-line chemotherapy Metastatic breast cancer Aged ≥65 years	PLD (n=38)	Median age: 75 years (65-86) ECOG PS: 0/1=77%	Primary: Toxicity and feasibility	Liposomal doxorubicin and capecitabine are both feasible options as first-line chemotherapy for elderly MBC patients. Toxicity was acceptable, mainly being fatigue, hand-foot syndrome, and mucositis
			Capecitabine (n=40)			

AC=doxorubicin plus cyclophosphamide; CMF=cyclophosphamide, methotrexate and 5-fluorouracil; PLD=pegylated liposomal doxorubicin; non-PLD=either metronomic cyclophosphamide and methotrexate (CM) or no chemotherapy; FEC=5-fluorouracil, epirubicin and cyclophosphamide; NCI=National Cancer Institute; SD=standard deviation; AE=adverse event; QoL=quality of life; OS=overall survival; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=overall response rate; TTP=time to progression; KPS=Karnofsky performance status; RR=response rate; MBC=metastatic breast cancer.

6.3 Efficacy evidence

Five RCTs[10,12,15,16,19] presented survival outcomes of interest, as detailed in Table 5. Efficacy data are limited because the primary focus of the studies was safety and tolerability.

6.3.1 Early breast cancer

Muss et al[16] compared capecitabine with standard chemotherapy (CMF or AC) and reported a relapse-free survival rate of 63% for capecitabine and 85% for standard chemotherapy at 3 years, with a hazard ratio (HR) of 2.09 (95% confidence interval [CI] 1.38 to 3.17; p<0.001). Overall survival at 3 years was 86% for patients in the capecitabine arm and 91% for patients in the standard chemotherapy arm. The results were statistically significant (HR 1.85 (95% CI 1.11 to 3.08), p=0.02).

Crivellari et al[10] compared pegylated liposomal doxorubicin (PLD) with non-PLD, and reported an HR of 0.78 (95% CI 0.65 to 0.94) for breast cancer-free interval at 3 years.

6.3.2 Advanced or metastatic breast cancer

Two trials[15,19] reported time to progression (TTP), which ranged from 3 months (CMF) to 7.8 months (gemcitabine plus vinorelbine); however, the 7.8 months recorded by Latorre et al[15] is questionable due to the small number of patients in the trial. Feher et al[12] reported progression-free survival (PFS) to be 3.4 months for gemcitabine and 6.1 months for epirubicin; however, the results were not statistically significant (HR 1.68; CI 1.34 to 2.09).

Three trials[12,15,19] reported data on overall survival (OS). The best results from each study are as follows: Latorre et al[15] reported 11.4 months for gemcitabine plus vinorelbine, O'Shaughnessy et al[19] reported 19.6 months for the capecitabine arm and Feher et al[12] reported 19.1 months for the epirubicin arm. Three trials[12,15,19] reported overall response rates (ORR), which ranged from 16% for CMF to 40.3% for epirubicin. Capecitabine achieved an ORR of 30%.

Table 5 Efficacy evidence, randomised controlled trials

Study	Intervention	Time to event (95% CI) Months	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
Early breast cancer							
Muss 2009[16]	Capecitabine	Relapse-free survival 63%	2.09 (1.38 to 3.17) p<0.001	86%[c]	1.85 (1.11 to 3.08) p=0.02	NR	NR
	Standard chemotherapy	Relapse-free survival 85%		91%[c]		NR	NR
Crivellari 2013[10]	PLD	Breast cancer-free interval at 3 years 0.78 (0.65 to 0.94)	NR	NR	NR	NR	NR
	Non-PLD	Breast cancer-free interval at 3 years 0.78 (0.68 to 0.93)	NR	NR	NR	NR	NR
Advanced or metastatic breast cancer							
O'Shaughnessy 2001[19]	Capecitabine	TTP: 4.1 (3.2 to 6.5)	NR	19.6	NR	30 (19 to 43)	NR
	CMF	TTP: 3 (2.4 to 4.8)	NR	17.2	NR	16 (5 to 33)	NR
Feher 2005[12]	Gemcitabine	TTP: 3.4 (2.8 to 3.8)	1.68 (1.34 to 2.09) p=0.0001	11.8 (9.4 to 14.0)	NR	16.4 (11.0 to 21.8)	p<0.0001
	Epirubicin	TTP: 6.1 (5.2 to 7.5)		19.1 (17.1 to censored data)	NR	40.3 (33.3 to 47.3)	
Latorre 2006 (abstract only)[15]	Gemcitabine plus vinorelbine	TTP: 7.8[a]	NR	11.4[d]	NR	27	NR
	Gemcitabine plus mitoxantrone	TTP: 6.4[b]	NR	10.1[e]	NR	42	NR

[a] 34 weeks (range 4 to 81); [b] 28+ weeks (range 0 to 174+); [c] OS at 3 years; [d] 50 weeks (range 4 to 136); [e] 44 weeks (range 13 to 174+)
PLD=pegylated liposomal doxorubicin; CMF=cyclophosphamide, methotrexate and 5-fluorouracil; TTP=time to progression; PFS=progression-free survival; OS=overall survival; ORR=overall response rate; NR=not reported; CI=confidence interval

6.4 Tolerability evidence

All trials reported at least one outcome of interest for tolerability. Details for both early and advanced or metastatic breast cancer are presented in Table 6.

6.4.1 Early breast cancer

Four trials[10,16,17,21] provided information relating to tolerability of treatment, compliance or serious AEs. The median duration of treatment cycles was relatively similar across the trials. In terms of treatment completion, Romieu et al[21] reported that 90% and 86% of patients completed the study, Muss et al[16] reported that persistence to six cycles was achieved by 65% and 83% of patients, and Crivellari et al[10] reported therapy completion rates of 68% and 83%.

Withdrawals or discontinuation rates were low. Romieu et al[21] reported that 7% of patients in one arm withdrew due to AEs. Nuzzo et al[17] reported that 19% and 15% of patients stopped treatment. Dose modifications due to AEs were reported for one patient in the Crivellari et al trial[10].

Nuzzo et al[17] demonstrated significantly higher rates of grade 3-4 AEs ($p=0.0002$) and haematological adverse events ($p\leq0.0001$) for CMF versus docetaxel, and Muss et al[16] reported rates of grade 3-4 AEs that were significantly higher for CMF (70%) versus capecitabine (33%). Romieu et al[21] treated patients with FEC-100 either with pegfilgrastim or pegfilgrastim only in the occurrence of a neutropenic event. The results suggest that the addition of pegfilgrastim reduced serious AEs considerably (10% vs 41%). Crivellari et al[10] compared PLD with either metronomic cyclophosphamide and methotrexate (CM) or no chemotherapy and reported grade 3 AEs of 51% and 34% respectively.

6.4.2 Advanced or metastatic breast cancer

Four trials[12,15,19,23] provided information relating to tolerability of treatment, compliance or serious AEs. Discontinuation of treatment due to lack of benefit or toxicity occurred in 24% of patients,[23] compared with 2.6% of treatment modification due to AEs in Crivellari et al.[10] Lower toxicity levels and lower rates of serious AEs were reported for capecitabine compared with PLD.[23] Serious AE rates were higher for patients in the gemcitabine arm (20.7%) compared with patients in the epirubicin arm (13.6%) although the difference was not statistically significant ($p=0.063$).[12] Epirubicin treatment was associated with a higher number of dose delays, albeit with a higher RDI of 90.6%.

Table 6 Tolerability evidence, 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
Early breast cancer				
Romieu 2007[21]	FEC with pegfilgrastim: Full dose all cycles=26/30 (87%), 95%CI (69-96) Cycles at full dose on schedule=164/172 (95%) 95%CI (91-98) RDI 100%=17 (57%) RDI 95%- <100%=9 (30%) RDI 90%- <95=2 (7%) RDI <90%=2 (7%) Completed study=28 (90%)	FEC with pegfilgrastim: Withdrawn due to consent=2 (6%) Withdrawn due to non-compliance=2 (6%)	FEC with pegfilgrastim: >5 days delay in any cycle=2 (7%) Dose reduction in any cycle=1 (3%) Both >5 days delay and dose reduction=1 (3%) Cycles: >5 days delay/dose change=8/172 (5%)	FEC with pegfilgrastim in cycle 1: Serious AEs=3 (10%)
	FEC with pegfilgrastim if neutropenic event: Full dose all cycles=20/29 (69%) 95%CI (49-85) Cycles at full dose on schedule=136/152 (89%) 95%CI (83-94) RDI 100%=7 (24%) RDI 95%-<100%=12 (41%) RDI 90%- <95%=6 (21%) RDI <90%=4 (14%) Completed study=25 (86%)	FEC with pegfilgrastim if neutropenic event: Withdrawn due to consent=1 (3%) Withdrawn due to AEs=2 (7%) Lost to follow-up=1 (3%)	FEC with pegfilgrastim if neutropenic event: > 5 days delay in any cycle=7 (24%) Dose reduction in any cycle=2 (7%) Both >5 days delay and dose reduction=0 (0%) Cycles: >5 days delay/dose change=16/152 (11%)	FEC with pegfilgrastim if neutropenic event in cycle 1: Serious AEs=9 (41%)
Nuzzo 2008[17]	CMF: (Cycles 1-4) Delivered day 1=197/212 (92.2%) Delivered day 8=190/212 (89.6%) Delivered day 15=NA (Cycles 5 and 6) Delivered day 1=20/26 (76.9%) Delivered day 8=19/26 (73.1%) Delivered day 15=NA	CMF: Stopped treatment=10/53 (19%) First cycle=1/53 (1.9%) Second cycle=5/52 (9.6%) Third cycle=2/47 (4.3%) Fourth cycle=0/45 (0%) Fifth cycle=2/11 (9.1%)	CMF: (Cycles 1-4) Cycles with dose reduction=11/212 (5.2%) (Cycles 5 and 6) Cycles with dose reduction=2/26 (7.7%)	CMF: Any grade 3-4=40 (75.5%) Haematological=37 (69.8%) Non-haematological=12 (22.6%)
	Docetaxel: (Cycles 1-4) Delivered day 1=177/192 (92.2%) Delivered day 8=175/192 (91.1%) Delivered day 15=157/192	Docetaxel: Stopped treatment=7/48 (15%) First cycle=5/48 (10.4%) Second cycle=0/43 (0%) Third cycle=0/43 (0%)	NR	Docetaxel: Any grade 3-4=19 (39.6%) (vs CMF p=0.0002) Haematological=4 (8.3%) (vs CMF p≤0.0001)

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
	(81.1%) (Cycles 5 and 6) Delivered day 1=16/18 (88.9%) Delivered day 8=15/18 (83.3%) Delivered day 15=12/18 (66.7%)	Fourth cycle=0/43 (0%) Fifth cycle=2/9 (22.2%)		Non-haematological=15 (31.2%) (vs CMF p=0.11)
Muss 2009[16]	Standard chemotherapy: CMF=62% received planned cycles. AC=92% received planned cycles Persistence to 6 cycles=65% Non-persistence to 6 cycles=35% Average adherence (all cycles)=97% <80% of total expected doses=5% AC: no data available	NR	NR	CMF: Grade 3-4=70% Non-haematological=41% toxic deaths=0 AC: Grade 3-4=60% Non-haematological=25% toxic deaths=0
	Capecitabine: 80% received planned cycles Persistence to 6 cycles=83% Non-persistence to 6 cycles=17% Average adherence (all cycles)=78% <80% of total expected doses=25%	NR	NR	Capecitabine: Grade 3-4=34% Non-haematological=33%. toxic deaths=2/307 (1%)
Crivellari 2013[10]	PLD: Median cumulative dose 144 mg/m^2 Began therapy=37 (97%) Completed therapy=25(68%)	14/77 (18%) were considered ineligible due to low creatinine clearance	PLD: Treatment modification due to AEs=1 (2.6%)	PLD: Grade 3 AE=19 (51%) After treatment completion: Grade 3 AE=15 (42%) Grade 4 AE=1 (2.6%)
	CM: Median cumulative dosing of C was 5600 mg (expected dose 5600 mg), and M was 155 mg (expected dose 160 mg) Began therapy=35 (100%) Completed therapy=29 (83%) 16 weeks of C without dose adjustment or omission=17 (49%) 16 weeks of M without dose adjustment or omission=15 (43%)		NR	CM: Grade 3 AE=12 (34%) After treatment completion: Grade 3 AE=12 (34%) Grade 4 AE=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
Advanced or metastatic breast cancer				
O'Shaughnessy 2001[19]	Capecitabine: Median duration of treatment=4 cycles Capecitabine: Compliance=99% Mean administered dose as a proportion of the planned dose week 3=0.97 6=0.95 9=0.88 12=0.86 15=0.77 18=0.80	Capecitabine: Discontinued due to AEs=16% Completed initial 18 week treatment period=25/93 (41%).	Capecitabine: Treatment interruption and/or dose modification due to AEs=34%	Capecitabine: Toxic deaths=3/61 (5%)
	CMF: Median duration of treatment=4 cycles Compliance=100%. Mean administered dose as a proportion of the planned dose week 3=1.00 6=0.98 9=0.99 12=0.97 15=1 00 18=1.00	CMF: Discontinued due to AEs=0% Completed initial 18 week treatment period=12/93 (38%)	CMF: Treatment interruption and/or dose modification due to AEs=9%	CMF: Toxic deaths=0/32 (0%)
Feher 2005[12]	Gemcitabine: RDI=86.9% (100 delays) Gemcitabine: Complete cycles=699 (185 patients) Incomplete cycle=5 patients	Gemcitabine: Discontinued due to AEs=6.1%	Gemcitabine: Dose delays=100 Doses reduced=7% Doses omitted=9%	Gemcitabine: Serious adverse events=20.7% Toxic deaths=3 (1.5%)
	Epirubicin: RDI=90.6% (169 delays) 917 cycles delivered to 192 patients.	Epirubicin: Discontinued due to AEs=8.5% (vs gemcitabine p=0.441)	Epirubicin: Dose delays=169 Doses reduced=5% Doses omitted=5%	Epirubicin: Serious adverse events=13.6% (vs gemcitabine p=0.063)
Latorre 2006 (abstract only)[15]	Gemcitabine plus vinorelbine: Total cycles=90 Mean cycles per patient=6 (1-11)	NR	NR	Gemcitabine plus vinorelbine: Toxic death=1%

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
	Gemcitabine plus mitoxantrone: Total cycles=93 Mean cycles per patient=6 (2-8)	NR	NR	Gemcitabine plus mitoxantrone: Toxic death=1%
Seynaeve 2012 (abstract only)[23]	NR	Liposomal doxorubicin: Discontinuation due to PD=34% Discontinuation due to intercurrent death=3% Discontinuation due to lack of benefit=24%	NR	Any grade 3-4=26 patients (33.3%) during 43 cycles (35%)
	NR	Capecitabine: Discontinuation due to PD=27.5% Discontinuation due to intercurrent death=8% Discontinuation due to lack of benefit=15%	NR	

CM=metronomic cyclophosphamide and methotrexate; PP=5-fluorouracil, epirubicin and cyclophosphamide; SP=5-fluorouracil, epirubicin and cyclophosphamide with pegfilgrastim; CMF=cyclophosphamide, methotrexate and 5-fluorouracil; RDI=relative dose intensity; PLD=pegylated liposomal doxorubicin; PD=progressive disease; AE=adverse event;AC=doxorubicin plus cyclophosphamide; NR=not reported

6.5 Comprehensive geriatric assessment and quality of life

Summary data relating to CGA and quality of life (QoL) are presented in Table 7. Detailed results are presented in Appendices 4 and 5.

6.5.1 Early breast cancer

Comprehensive geriatric assessment

Romieu et al[21] and Nuzzo et al[17] both used CGAs to measure outcomes, with changes from baseline scores recorded at intervals. Nuzzo et al[17] used the Activities of Daily Living (ADL) and Instrumental ADL (IADL) tools, and Romieu et al[21] used the Vulnerable Elders Survey-13 (VES-13).

Quality of life, early breast cancer

Two RCTs reported QoL outcomes. Muss et al[16] used two measures, the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30) and the Hospital Anxiety and Depression Scale (HADS), whereas Crivellari et al[10] used three measures, the Linear Analogue Self-Assessment (LASA) indicators, physician-administered cognitive functioning, and physician-administered VES.

6.5.2 Advanced or metastatic breast cancer

None of the trials reported use of CGA. Feher et al[12] reported QoL outcomes using EORTC QLQ-C30 and QLQ-BR23 and reported that only six measures showed a change from baseline for between-arm differences.

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

Study	Comprehensive geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
Early breast cancer				
Romieu 2007[21]	VES-13	Used as outcome measure with baseline data and change in score through treatment	NR	NR
Nuzzo 2008[17]	IADL ADL	Used as outcome measure with baseline data and change in score through treatment	NR	NR
Muss 2009[16]	NR	NR	EORTC QLQ-C30 HADS total (≥15 indicates clinically important anxiety and depression) Linear mixed-effect models used	Patients treated with capecitabine had a significantly better global QoL score at midtreatment ($p<0.001$) and end of treatment ($p<0.001$), fewer systemic treatment-related AEs at midtreatment ($p<0.001$) and end of treatment ($p<0.001$), and a lower HADS total score at midtreatment ($p<0.001$) and end of treatment ($p<0.001$) than those treated by standard chemotherapy
Crivellari 2013[10]	NR	NR	Self-reported QoL with LASA indicators (range 0-100) Physician-administered cognitive functioning (Mini-Cog test; range 0-5) Physician-administered physical functioning (VES; range 0-10)	Patients on PLD reported worse QoL scores than those on non-PLD for all measures. Similarly, patients receiving PLD indicated worse cognitive and physical functioning
Advanced or metastatic breast cancer				

Feher 2005[12]			EORTC QLQ-C30 QLQ-BR23	A total of 248 patients (120 gemcitabine and 128 epirubicin) were included in the QoL analysis. Between-arm differences in change from baseline were noted in six of the 23 QoL scales. Gemcitabine-treated patients reported greater deterioration of physical functioning, while epirubicin-treated patients reported greater increases in nausea/vomiting, greater deterioration of body image, and greater incidence and/or severity of side-effects. However, epirubicin-treated patients also reported greater pain and arm symptom relief

VES=Vulnerable Elders Survey; IADL=Instrumental Activities of Daily Living; ADL=Activities of Daily Living; HADS=Hospital Anxiety and Depression Scale; LASA=Linear Analogue Self-Assessment; AE=adverse event;

6.6 Discussion

Although eight RCTs were included, the evidence suggests that there is a lack of quality RCTs designed to recruit only older patients. The included trials were of poor methodological quality overall; adequate randomisation was reported in only three trials,[17,19,21] and none of the trials were considered to have adequate concealment of allocation. Only one trial[19] reported that assessors were blinded to treatment allocation. Two trials[15,23] were reported in abstract form only, and data were limited. The trials were relatively small, with only three[12,16,17] trials randomising more than 100 patients.

The patients included in the trials were predominantly fitter patients, with better PS scores than those seen in routine clinical practice, meaning the results could be generalised to reflect fit older people. Each trial used a different definition of older, with O'Shaughnessy et al[19] recruiting patients aged 55 or older and Latorre et al[15] recruiting patients aged 70 or over, which presents a significant age range to consider. However, the range of median ages of patients across trials was narrow (67.5 to 79 years).

The included trials reported a variety of outcome measures, which clearly differ between early and advanced or metastatic breast cancer, with outcomes for early breast cancer focussing on how long the patient remains cancer free, and outcomes for advanced or metastatic breast cancer measuring how well (or poorly) the cancer is controlled before either death or disease progression. Of the five trials[10,12,15,16,19] that reported efficacy outcomes, only one trial[16] presented statistically significant results, which showed that capecitabine performed better than standard chemotherapy in terms of relapse-free survival for patients with early breast cancer. The data presented suggest that older people can tolerate chemotherapy, and that newer regimens such as capecitabine cause fewer AEs than older regimens such as FEC-100 or CMF.

For both early breast cancer and advanced or metastatic breast cancer RCTs, there was a lack of data reporting on the use of QoL and CGA tools. None of the trials used CGA to determine a patient's eligibility for inclusion in the trial; the focus in the studies was on applying CGA tools and using the results as measurable outcomes. There seems to be some cross-over between CGA measures and QoL measures, with the VES used as both QoL and CGA in two different trials.[10,21]

The authors' conclusions generally support the use of chemotherapy in elderly people with breast cancer, and generally indicate that chemotherapy is feasible, efficacious and tolerable.

7 SUBGROUP ANALYSES OF RANDOMISED CONTROLLED TRIALS

Five RCTs (reported in seven publications[24-30]) met the inclusion criteria for the reporting of subgroup analyses of older patients. Details of study characteristics are presented in Table 8.

7.1 Study characteristics

7.1.1 Overview

Three studies[25,28,30] reported subgroup data from phase III RCTs, one study[24] reported data from a phase II RCT, and in one study[27] the phase was not reported. Four studies were multicentre.[24,27,28,30] One study was international[28] and the rest were conducted in Germany,[27,30] the USA,[25] and Belgium.[24] Two studies were funded by pharmaceutical companies.[25,28] With the exception of Jones et al,[25] none of the subgroup analyses were planned as part of the original RCT design.

The proportion of older patients within the studies is presented, where available, alongside details of the interventions administered. The proportion of older patients varied from 15%[25] to 43%.[24] The PS was reported in three studies[27,28,30] and was broadly similar, with most patients being ECOG 0-1 or KPS >80.

7.1.2 Early breast cancer

Two studies[25,27] focussed on the treatment of early breast cancer. Jones et al[25] was a subgroup analysis from a large RCT that randomised 1016 patients, and Kummel et al[27] was a subgroup analysis of a smaller RCT that randomised 211 patients. The proportion of older patients in both RCTs was small: less than 20% in Jones et al[25] and less than 30% in Kummel et al.[27] Only the study by Jones et al[25] included a planned subgroup analysis.

The mean age of patients in the Kummel et al study[27] was 64.7 years in both arms, and the median age of patients in Jones et al[25] was 68 and 69 years, respectively. The PS was reported in one study,[27] with the majority of patients scoring ECOG PS 0.

Authors' conclusions from both studies suggest that chemotherapy for older patients with early breast cancer can be tolerated.

7.1.3 Advanced or metastatic breast cancer

Three studies[24,28,30] investigated chemotherapy for advanced or metastatic breast cancer. Pivot et al[28] conducted a subgroup analysis of a large RCT that randomised 489 patients, whereas the other two studies[24,30] were from small RCTs that randomised 70 and 102 patients, respectively. In Pivot et al,[28] the proportion of older patients was less than 20%, and in Beuselinck et al[24] the proportion of older

patients in each arm was 36% and 43%, respectively. None of the included studies had stratified patients by age at the time of randomisation.

Median age across the studies varied from 67 to 75.5 years. In Pivot et al,[28] more than 50% of the patients in both arms had an ECOG PS of 0. Stemmler et al[30] reported a median KPS of 80 in each arm.

The authors' conclusions indicate that chemotherapy is a feasible treatment option for older people with advanced or metastatic breast cancer, and the results for the older subgroups and overall populations were similar.

Table 8 Study characteristics, subgroup analyses of randomised controlled trials

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Early breast cancer						
Kummel 2006[27]	Multicentre Open-label Germany June 1996-Dec 2000 Follow-up to 5 years after inclusion Patients not stratified by age at randomisation	Adjuvant chemotherapy Primary resected BC Older defined as ≥ 60 years	Dose-dense regimen epirubicin and paclitaxel followed by CMF Older patients=25/104 (24%)	Mean age (SD): 64.7 years (3.2) ECOG PS: 0=71 (93%) 1=5 (7%)	Primary: Feasibility, safety, tolerability	This study demonstrates that a dose-dense regimen combining epirubicin and paclitaxel can be administered to patients ≥60 years of age with a tolerable safety profile
			Conventional regimen epirubicin and cyclophosphamide followed by CMF Older patients=27/107 (27%)	Mean age (SD): 64.7 years (3.3) ECOG PS: 0=69 (90%) 1=8 (10%)		
Jones 2009[25]	Phase III Single centre USA Sanofi-Aventis, Bridgewater, NJ 7 year follow-up Patients were stratified by age and nodal status at randomisation	Adjuvant chemotherapy Women with early breast cancer (stages I-III) Older defined as ≥ 65 years	Standard doxorubicin and cyclophosphamide (TC) Older patients=82/510 (16%)	Median age: 68 years (65-77)	Primary: DFS, OS	With longer follow-up, four cycles of TC was superior to standard AC (DFS and OS) and was a tolerable regimen in both older and younger patients
			Docetaxel plus cyclophosphamide (AC) Older patients=78/506 (15%)	Median age: 69 years (65-77)		

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Advanced or metastatic breast cancer						
Beuselinck 2010[24]	Phase II Multicentre 6 centres in Belgium 2002-2005 Patients not stratified by age at randomisation	Mixed settings Metastatic disease Older defined as >70	Paclitaxel Older patients=12/33 (36%)	Median age: 75.3 years	Primary: Anti-tumour activity Secondary: Toxicity, TTP	In patients with MBC unfit for 3-weekly docetaxel or paclitaxel, weekly administration of either compound may certainly be considered. They display different, but acceptable toxicity profiles, with levels of anti-tumoural efficacy comparable to those previously reported for 3-weekly regimens
			Docetaxel Older patients=16/37 (43%)	Median age: 75.5 years		
Stemmler 2010[30]	Multicentre Phase III Germany July 2001-August 2008 Follow-up: Mean=14.4 months (range 1.2-77.7) Patients not stratified by age at randomisation	First-line chemotherapy Metastatic disease Chemotherapy naïve Older defined as >60 years	Weekly docetaxel (n=48) Older patients=NR	Median age: 73 years (58-84) Median KPS: 80 (60-100)	Primary: Haematotoxicity Secondary: TTP, OS	The present data support the feasibility of both weekly and 3-weekly application of docetaxel. As expected, severe leukopenia seems avoidable in weekly scheduled single-agent docetaxel and may serve as an important treatment option, particularly in elderly patients and patients with a reduced PS
			3-weekly docetaxel (n=54) Older patients=NR	Median age: 70.5 years (60-82) Median KPS: 80 years (60-100)		
Pivot 2011[28]	Phase III AVADO trial Multicentre International France, Germany, Canada, Portugal, Italy, Spain, Switzerland, Taiwan, UK F. Hoffmann-La Roche Ltd 25 months follow-up Patients not stratified by	First-line chemotherapy Women with HER2-negative locally recurrent or metastatic disease Older defined as >65	Docetaxel plus placebo Older patients=38/241 (16%)	Median age: 67 years (65-83) ECOG PS: 0=22 (58%) 1=14 (37%)	Primary: PFS Secondary: ORR, TTF, OS, safety	In this exploratory subgroup analysis in AVADO, bevacizumab plus docetaxel showed efficacy in elderly patients similar to the overall study population. There were no unexpected safety signals in patients aged 65 years or older
			Docetaxel plus bevacizumab (7.5 mg/kg) Older patients=41/248	Median age: 69 years (65-83) ECOG PS: 0=27 (56%)		

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	age at randomisation		(17%)	1=21 (44%)		
			Docetaxel plus bevacizumab (15 mg/kg), 48/247 (19%)	Median age: 68 years (65-76) ECOG PS: 0=27 (56%) 1=21 (44%)		

TC=docetaxel plus cyclophosphamide; AC=Standard doxorubicin and cyclophosphamide; DFS=disease-free survival, OS=overall survival; ORR=overall response rate; TTF=time to treatment failure; TTP=time to progression; KPS=Karnofsky performance status; SD=standard deviation; ECOG PS=Eastern Cooperative Oncology Group performance status

7.2 Efficacy evidence

Results for PFS, TTP, OS and ORR are presented in Table 9.

7.2.1 Early breast cancer

Neither of the early breast cancer studies reported efficacy outcomes of interest; Kummel et al[27] reported outcomes focussed on tolerability and Jones et al[25] did not provide a detailed breakdown of efficacy outcomes by age, only by overall population.

7.2.2 Advanced or metastatic breast cancer

Three subgroup analyses[24,28,30] reported efficacy outcomes of interest. All three studies focussed on patients with locally advanced or metastatic disease. Two of the studies presented comparisons between older and younger patients across study arms. Beuselinck et al[24] and Stemmler et al[30] reported TTP, which ranged from 2.9 months to 6.3 months, both for docetaxel regimens. Beuselinck et al[24] reported a 4.8 month TTP for paclitaxel. Pivot et al[28] presented data for patients aged >65 compared with the overall ITT population and results were similar for older and younger patients. There was one statistically significant result for the ITT population comparing docetaxel plus bevacizumab with placebo (HR 0.67 (95% CI 0.54 to 0.83) p<0.001).[28]

The OS varied from 12.8 months for docetaxel[24] to an OS estimate of 25 months for docetaxel plus bevacizumab.[28] In terms of ORR, Pivot et al[28] reported rates of 44.7% and 50% for docetaxel plus placebo and docetaxel plus bevacizumab, respectively.

Stemmler et al[30] reported a much higher ORR for weekly docetaxel compared with 3-weekly docetaxel, which was statistically significant: 42.6% versus 22.9% p=0.039.

Table 9 Efficacy evidence, subgroup analyses of randomised controlled trials

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR (95% CI) %	Hazard ratio (95% CI) P value
Advanced or metastatic breast cancer							
Beuselinck 2010[24]	Paclitaxel	TTP: 4.8 (3.4 to 6.6)	NR	12.8 (6.5 to 79.0)	NR	NR	NR
	Docetaxel	TTP: 2.9 (1.9 to 6.7)	NR	18.1 (4.4 to 11.7)	NR	NR	NR
Stemmler 2010[30]	Docetaxel q1w	TTP: 5.4 (0.7 to 48.2)	p=0.91	22.7 (1.8 to 41.4)	p=0.24	22.9 (12.0 to 37.3)	p=0.039
	Docetaxel q3w	TTP: 6.3 (0.4 to 20.1)		15.8 (1.2 to 32.8)		42.6 (29.2 to 56.8)	
Pivot 2011[28]	Docetaxel+placebo	PFS: Stratified analysis: >65=7.6 ITT=8.1 Unstratified analysis: >65=7.7 ITT=8.2	NR	OS Estimate=22.5	NR	44.7 (28.6 to 61.7)	NR
	Docetaxel+bevacizumab (7.5 mg/kg)	PFS: Stratified analysis: >65=9 ITT=9 Unstratified analysis: >65=9 ITT=9	Stratified analysis: >65: 7.5 mg/kg vs placebo 0.76 (0.46 to 1.262) p=0.35 Unstratified analysis: >65: 7.5 mg/kg vs placebo 0.83 (0.518 to 1.315) p=0.48	NR	NR	50 (35.2 to 64.8)	NR
	Docetaxel+bevacizumab (15 mg/kg)	PFS: Stratified analysis: >65=10.3 ITT=10 Unstratified analysis: >65=10.3 ITT=10.1	Stratified analysis: >65: 15 mg/kg vs placebo 0.63 (0.383 to 1.032), p=0.07 ITT: 15 mg/kg vs placebo 0.67 (0.54 to 0.83)	OS Estimate=25	NR	36.6 (22.1 to 53.1)	NR

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR (95% CI) %	Hazard ratio (95% CI) P value
			p=<0.001 Unstratified analysis: >65: 15 mg/kg vs placebo 0.68 (0.428 to 1.076) p=0.095				

TTP=time to progression; PFS=progression-free survival; ITT=intention to treat; NR=not reported; ORR=overall response rate; CI=confidence interval; OS=overall survival

7.3 Tolerability evidence

Table 10 summarises the evidence relating to tolerability from both early and advanced or metastatic breast cancer studies.

7.3.1 Early breast cancer

Two studies[25,27] reported data regarding tolerability. The discontinuation rates reported by Kummel et al[27] were 4% for both arms, dose reductions were 4% for older patients and 14% for younger patients, and the older patients had more cycle delays. Adverse events at grades 3-4 were reported by Kummel et al,[27] and showed higher rates of neutropenia and leukopenia in the older subgroup.

7.3.2 Advanced or metastatic breast cancer

Three studies[24,28,30] reported data regarding tolerability. The data in Pivot et al[28] suggest that older patients received a median dose intensity of >90% across all arms. Stemmler et al[30] reported that both arms received >90% of the intended drug. Pivot et al[28] reported discontinuations for younger and older patients, with the rates for discontinuation in the older group being almost double those in younger patients in all arms. Beuselinck et al[24] reported that 36% discontinued treatment due to toxicity, and there were two toxic deaths.

Table 10 Tolerability evidence, subgroup analyses of 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
Early breast cancer				
Kummel 2006[27]	Dose-dense epirubicin and paclitaxel followed by CMF: Maximum duration of treatment=7 cycles ≥60 receiving 7 cycles=25 (100%) <60 receiving 7 cycles=75 (95%)	<60 1 patient (<1%) refused further treatment after first cycle Rate of discontinuation for both age groups=4%	Dose reductions: ≥60=4% <60=14% Cycle delays: ≥60=13% <60=7% Cycle delay due to delayed haematological recovery: ≥60=22% (8/9 cases in dose-dense) <60=15%	Grade 3 and 4 leukopenia: ≥60=26% <60=12% Grade 3 and 4 neutropenia: ≥60=33% <60=25%
	Conventional epirubicin and paclitaxel followed by CMF: Maximum duration of treatment=7 cycles ≥60 receiving 7 cycles=24 (89%) <60 receiving 7 cycles=79 (99%)	Rate of discontinuation for both age groups=4%		≥60 reasons for discontinuation were death and hypersensitivity reaction to methotrexate. Grade 4 non-haematological toxicities: ≥60 with nausea=1 <60 with bone pain=1 Grade 3 cardiotoxicity: ≥60=1
Jones 2009[25]	NR	NR	NR	Standard doxorubicin and cyclophosphamide (AC): Three late deaths without relapse, probably related to treatment
Advanced or metastatic breast cancer				
Beuselinck 2010[24]	Paclitaxel: Median chemotherapy administrations=11-32 Average duration=101-263 days Mean delivered dose per cycle=129 mg (76 mg/m^2) Median dose-intensity to 8 weeks=62 mg/(m^2 week) Total dose intensity=56.6 mg/(m^2 week)	NR	Dose reductions=6/33 Interruption due to toxicity=12/33 (36%)	NR
	Docetaxel: Median chemotherapy administrations=8-22 Average duration=71-191 days Mean delivered dose per cycle=57.5 mg (34.4 mg/m^2)	NR	Dose reductions=6/37 Interruption due to toxicity=17/37 (45%)	Toxic death=2 (both older)

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
	Median dose intensity to 8 weeks=29.5 mg/(m^2 week) Total dose intensity=27 mg/(m^2 week)			
Stemmler 2010[30]	Weekly docetaxel: Median duration of treatment=4 cycles (range 1-8) Intended drug delivery=92.8%	NR	Dose reductions=22 (11.83%) Delayed doses=22 (11.83%) Omitted doses=16 (8.60%)	Leukopenia=4.2%
	3-weekly docetaxel: Median duration of treatment=6 (range 1-8) Intended drug delivery=95.7% (p > 0.05)	NR	Dose reductions=26 (8.81%) (p>0.05) Delayed doses=23 (7.80%) (p>0.05) Omitted doses=0 (p<0.001)	Leukopenia=51.9% (p<0.0001)
Pivot 2011[28]	Docetaxel+placebo: Median dose intensity Placebo: ≥65=100%; ITT=98% Docetaxel: ≥65=97.2; ITT=95%	Discontinuations due to AEs: ≥65=22% <65=12%	NR	Grade 3=67%
	Bevacizumab 7.5+docetaxel: Median dose intensity: Bevacizumab: ≥65=99.5%; ITT=97% Docetaxel: ≥65=91.1%; ITT=91%	Discontinuations due to AEs: ≥65=26% <65=14%	NR	Grade 3=78%
	Bevacizumab 15+docetaxel: Median dose intensity: Bevacizumab: ≥65=99.2%; ITT=96% Docetaxel: ≥65=95.5%; ITT=89%	Discontinuations due to AEs: ≥65=25% <65=9%	NR	Grade 3=75%

ITT=intention to treat, NR=not reported; AE=adverse event

7.4 Comprehensive geriatric assessment and quality of life

None of the included studies presented data relating to CGA or QoL.

7.5 Discussion

Of the five[24-30] subgroup studies included in the review, only one[25] subgroup analysis was planned in accordance with the original RCT design and stratified patients by age at the time of randomisation. Generally, the proportion of older patients in the studies was low, and the study results were mostly derived from small RCTs.

In terms of efficacy, the three studies[24,28,30] that focussed on advanced or metastatic breast cancer provided results for the outcomes of interest, with one statistically significant result for ORR favouring weekly docetaxel over 3-weekly docetaxel.[30] Pivot et al[28] reported a significant result for PFS in the ITT population, which favoured docetaxel plus bevacizumab over placebo.

The data regarding tolerability are difficult to interpret given the variability of outcome measures. Two studies[27,28] compared discontinuation rates between older and younger patients; the data suggest that older patients have a higher rate of discontinuation than younger patients. One study[27] compared dose reductions and showed that older patients had lower rates of dose reductions than younger patients. One study[27] presented comparisons of AEs, which showed that older patients had higher rates of leukopenia and neutropenia than younger patients.

None of the studies utilised CGA tools or QoL measures.

In general, the authors' conclusions suggest that chemotherapy for older patients is tolerable and efficacious, and that older patients did not experience poorer health outcomes than younger patients.

8 POOLED ANALYSES

8.1 Study characteristics

A total of seven pooled analyses were included and reported in nine publications.[31-39] The study by Vahdat et al[39] is reported in abstract form only. All studies appeared to use individual patient data (IPD) in their analyses, but none of the included studies stratified patients by age at the time of randomisation. Study characteristics are presented in Table 11.

8.1.1 Overview

There were four retrospective analyses of data from RCT trials[32,33,36,38] and three retrospective cohorts.[31,34,39] Three were multicentre studies[32,38,39] and one was an international study.[32] Three studies were funded by pharmaceutical companies,[31,36,39] three by research grants,[33,34,38] and one study did not report its funding source.[32] The smallest study was Biganzoli et al,[32] which analysed 65 patients aged over 70 years, and the largest study was the EBCTCG study,[33] which analysed 3346 patients.

One study[34] focused on first- and second-line chemotherapy, and one study[31] used mixed settings. The line of treatment was unclear in five studies.[32,33,36,38,39] The PS was reported in only three studies,[31,32,34] and there was little variation across these studies, with only a small proportion of patients with an ECOG PS >2.

8.1.2 Early breast cancer

Three studies[33,36,38] focussed on the treatment of early breast cancer and derived data from RCTs. The proportion of older patients in each study was relatively small. All studies appear to have used IPD. None of the studies reported PS data.

According to the authors' conclusions, chemotherapy for the treatment of early breast cancer in older patients is a safe and feasible option, but older patients may not derive as much survival benefit as their younger counterparts.

8.1.3 Advanced or metastatic breast cancer

Four studies[31,32,34,39] analysed data from studies of advanced or metastatic breast cancer. Data collected in Biganzoli et al[32] were derived from RCTs, and three studies[31,34,39] pooled data from phase II/III studies. The proportion of older patients was small, and all studies appear to have used IPD.

The authors' conclusions suggest that the safety profile and efficacy of the treatments are similar for both older and younger patients.

Table 11 Study characteristics, pooled analyses

Study	Study details	Population	Intervention, n	Purpose	Authors conclusions
Early breast cancer					
Muss 2007[38]	Retrospective analysis of 3 RCTs[40,41] Multicentre USA Funded by numerous research grants 1985-1999 No stratification by age Appear to have used IPD	Adjuvant chemotherapy for node-positive breast cancer ≥65 years=458 (7%) >70 years=144 (2%)	CALGB 8541: High dose CAF or Mid-/low-dose CAF CALGB 9344: three dose levels of doxorubicin and a fixed dose of cyclophosphamide with or without paclitaxel. CALGB 9741: cyclophosphamide, doxorubicin, and paclitaxel N=6642	Assess older patients' response to more aggressive systemic adjuvant chemotherapy regimens	Elderly patients treated with newer adjuvant chemotherapy regimen derive the same benefits from newer chemotherapy regimens as younger patients but should be cautioned about the increased risk of toxicity and treatment-related death
EBCTCG 2008[33]	Retrospective analysis of 96 trials Funded by UK Medical Research Council, Cancer Research UK 1975-1996 No stratification by age Used IPD	Early breast cancer Polychemotherapy and tamoxifen <60 years=14,464 60-69 years=2599 (13%) ≥70 years=747 (4%)	Varied None of the studies used taxane based treatments N=19,746	Meta-analysis of all randomised trials of the treatment of early breast cancer. This report is the 5th since the inception of the collaborative	Older adjuvant polychemotherapies are safe (i.e. have little effect on mortality other than breast cancer). Patients aged 60-69 did not derive as much survival benefit as younger women
Loibl 2008[36]	Analysis of 4 RCTs[42-45] Germany Funded by Sanofi-Aventis, Germany; Amgen, Europe No stratification by age Appear to have used IPD	Primary breast cancer ≥65=622 (15%)	Combination docetaxel+doxorubicin+cyclophosphamide Sequence schedule (doxorubicin[epirubicin] cyclophosphamide) followed by docetaxel or paclitaxel Combination dose-dense doxorubicin/docetaxel Sequence dose-dense epirubicin/paclitaxel N=4227	To assess adverse events for patients <60, 60-64 and >65	The present pooled analysis of a substantial cohort of older primary breast cancer patients demonstrates that taxane-containing (neo)adjuvant chemotherapy is feasible in older patients and that toxicity can be reduced by sequential therapy regimens

Study	Study details	Population	Intervention, n	Purpose	Authors conclusions
Advanced or metastatic breast cancer					
Biganzoli 2007[32]	Retrospective analysis of RCTs[46,47] Multicentre International Italy, UK, Australia, Switzerland, Belgium No stratification by age Appear to have used IPD	Metastatic breast cancer >70 years=65 (48%) ECOG ≥2=14%	PLD every 6 weeks PLD every 4 weeks N=136	Compare the safety and efficacy of two regimens of PLD, comparing older and younger patients	In patients >70 no dependence was found between the incidence of grade 3–4 toxicity or antitumour activity and patients' baseline performance status, number and severity of comorbidities, or number of concomitant medications
Vahdat 2011[39] (abstract only)	Retrospective analysis of phase II studies – references not provided Multicentre Funded by Bristol-Myers Squibb Stratification by age unclear Appear to have used IPD	Metastatic breast cancer ≥65 years=251 (13%)	Ixabepilone plus capecitabine Capecitabine N=1973	To determine the efficacy and safety of ixabepilone plus capecitabine vs capecitabine alone in elderly patients compared with the overall population	The safety profile of the treatments was similar in patients over and under 65 years
Aapro 2011[31]	Retrospective analysis of patients ≥65 years from 2 studies (phase II[48] and III[49]) USA Funded by Abraxis and Celgene No stratification by age Appear to have used IPD	Mixed settings Metastatic breast cancer ≥65=114 (15%) ECOG ≥2=8%	Nab-paclitaxel Docetaxel Solvent-based paclitaxel N=147/754 (>65=19.4%)	Post-hoc analysis of 2 studies investigating the safety and efficacy of weekly and 3-weekly treatments in older patients with MBC compared with q3w solvent-based paclitaxel and docetaxel	Weekly treatments were safer and more efficacious compared with the 3-weekly schedule in combination with solvent-based taxanes in older patients with MBC

Study	Study details	Population	Intervention, n	Purpose	Authors conclusions
Litchman 2012[34]	CALGB 9342 and 9840[50,51] USA Funded by the National Cancer Institute No stratification by age Appear to have used IPD	First (57%) and second (43%) line chemotherapy ≥65=272 (26%) ECOG ≥2 <64 years 1.5% ≥65 years 2.5%	Weekly paclitaxel or paclitaxel every 3 weeks N=1048	To determine efficacy and tolerability of paclitaxel in older patients	Older women with breast cancer derive similar efficacy from treatment as younger women but are at increased risk for specific toxic effects

CAF=cyclophosphamide, doxorubicin and fluorouracil; PLD, pegylated liposomal doxorubicin; RCT=randomised controlled trial; ECOG=Eastern Cooperative Oncology Group; IPD=individual patient data; CALGB=Cancer and Leukemia Group B; MBC-metastatic breast cancer

8.2 Efficacy evidence

Outcomes relating to PFS, OS, and ORR and presented in Table 12. The bold text indicates where comparisons have been made between older and younger patients.

8.2.1 Early breast cancer

None of the studies of early breast cancer reported survival outcomes because the primary outcomes of these studies were related to feasibility and toxicity.

8.2.2 Advanced or metastatic breast cancer

Four studies[31,32,34,39] provided survival data, and three of the studies compared older patients with a younger population.[32,34,39] All studies focussed on patients with locally advanced or metastatic disease. Where comparisons were made between older and younger patients, results were broadly similar. None of the results were statistically significantly different.

Two studies[32,39] reported PFS which ranged from 3.9 months for capecitabine[39] to 5.6 months for PLD[32] in older patients. Overall, a longer PFS was seen in the younger population across all treatment regimens.

Vahdat et al[39] also reported OS, which was slightly higher in the younger population. Adding ixabepilone to capecitabine increased OS from 12.2 months to 13.9 months in the over 65s.[39] The ORRs were also higher with this treatment, increasing from 19% to 37%.[39]

Table 12 Efficacy evidence, pooled analyses

Study	Intervention	Median PFS (95% CI) Months	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR (95% CI) %	Hazard ratio (95% CI) P value
Advanced or metastatic breast cancer							
Biganzoli 2007[32]	<70 years (PLD every 4/6 weeks)	**5.9 (5.4 to 8.3)**	NR	NR	NR	NR	NR
	≥70 years (PLD every 4/6 weeks)	**5.6 (5.1 to 7.3)**	NR	NR	NR	NR	NR
Vahdat 2011[39] (abstract only)	Ixabepilone plus capecitabine <65 vs ≥65 years	**5.6 vs 5.5**	NR	**14.7 vs 13.9**	NR	**42 vs 37**	NR
	Capecitabine <65 vs ≥65 years	**4.2 vs 3.9**	NR	**13.0 vs 12.2**	NR	**26 vs 19**	NR
Aapro 2011[31]	Nab-paclitaxel Docetaxel Solvent-based paclitaxel	Range 3.5 to 18.9	NR	Range 12.8 to 21.7	NR	NR	NR
Litchman 2012[34]	Paclitaxel <55 vs ≥65 years	NR	**1.14 (0.96 to 1.35) p=0.31**	NR	**1.07 (0.90 to 1.27) p=0.73**	NR	NR
	Paclitaxel 55 to 64 vs ≥65 years	NR	**1.08 (0.90 to 1.30)**	NR	**1.04 (0.86 to 1.25)**	NR	NR

N.B. Bold text indicates where comparisons have been made between older and younger patients

PFS=progression free survival; CI=confidence interval; OS=overall survival, ORR=overall response rate; NR=not reported; PLD=pegylated liposomal doxorubicin

8.3 Tolerability evidence

Outcomes relating to tolerability are presented in Table 13.

8.3.1 Early breast cancer

Two studies[36,38] provided information regarding treatment tolerability, compliance and serious AEs. Muss et al[38] demonstrated that early discontinuation of treatment increased with advancing age, with an odds ratio of 2.48. Adverse events were fairly similar between older and younger patients.

The combination chemotherapy reported by Loibl et al[36] also demonstrated an increase in delayed administration or dose reductions with increasing age. Discontinuations were highest in patients aged over 64 compared with those aged under 60 (18.7% vs 11.8%), as were the percentages of grade 3-4 AEs. Both of the studies[36,38] compared data for young versus older patients, and the results for discontinuations were similar, suggesting an acceptable tolerability for older patients.

8.3.2 Advanced or metastatic breast cancer

Three studies[31,32,34] provided information regarding treatment tolerability, compliance and serious AEs. Biganzoli et al[32] reported an increase in dose reductions and cycle delay for both treatment regimens in patients over 70, along with an increase in grade 3-4 adverse events. Delivery of PLD every 4 weeks instead of every 6 weeks decreased febrile neutropenia from 12% to 0% in the older population.

Aapro et al[31] compared various chemotherapy regimens; solvent-based docetaxel caused the highest amount of therapy discontinuation (37%) and grade 3-4 adverse events (91%). Nab-paclitaxel had the lowest number of discontinuations (6%) and the lowest number of AEs (34%).

Table 13 Tolerability evidence, pooled analyses

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
Early breast cancer				
Muss 2007[38]	NR	Discontinued prior to completion Total 210 (3%) ≤50=2% 51-64=4% >64=6% 50 vs >64 treatment stoppage OR: 2.48; 95%CI, 1.57 to 3.91 For each regimen, early discontinuation increased linearly with advancing age (p=0001)	NR	% Grade 4: Any haematological 51-64 years=17% 65+ years=18% % Grade 3-4: Any non-haematological 51-64 years=19% 65+ years=17%
Loibl 2008[36]	NR	<60=11.8% 61-64=17.2% >64=18.7%	Delay in administration: <60=9% 61-64=12.6% >64=13.7% Dose reduction: <60=5.1% 61-64=6.7% >64=8.1%	Leukopenia: <60=55.3% >64=65.5% Neutropenia: <60=46.9% >64=57.4%
Advanced or metastatic breast cancer				
Biganzoli 2007[32]	Median cycles (range): PLD: every 6 weeks <70 years:6 (2-9) Consent withdrawal=3/39	NR	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
	PLD: every 6 weeks ≥ 70 years: 4 (1-8) Consent withdrawal=5/34	NR	NR	NR
	PLD: every 4 weeks <70 years:1(1-14) Consent withdrawal=3/29	NR	NR	NR
	PLD: every 4 weeks ≥ 70 years: 4(1-15) Consent withdrawal=5/28	NR	NR	NR
Aapro 2011[31]	Median cycles (range): Nab-paclitaxel 300 mg/m^2 :6 (1-21) Nab-paclitaxel 100 mg/m^2: 6.5 (2-22) Nab-paclitaxel 150 mg/m^2: 6 (2-17) Solvent-based Docetaxel 100 mg/m^2: 7 (1-13) Solvent-based paclitaxel 175 mg/m^2: 5 (1-18) Nab-paclitaxel 260 mg/m^2: 4.5 (1-10)	NR	NR	NR
Litchman 2012[34]	Median number of cycles: <55=6 (1-72) 55-64=6 (1-55) ≥65=7 (1-44)	NR	NR	NR

NR=not reported; OR=odds ratio; CI=confidence interval; PLD=pegylated liposomal doxorubicin

8.4 Comprehensive geriatric assessment and quality of life

None of the pooled analyses presented data relating to the use of either CGA or QoL measures.

8.5 Discussion

In the pooled analyses, eight different regimens were used, either as a single treatment[31,32,34,39] or in combination.[36,38,39] The majority of studies appear to have used IPD, which is to be applauded and a research direction that should be encouraged. With the exception of the ongoing EBCTCG[33] project, the samples were, of necessity, convenience samples. The primary studies included in the pooled analyses did not stratify the patients by age, and therefore the findings need to be viewed with caution as study randomisation has been broken.

Examination of the study results and the authors' conclusions vary. The analyses with fewer studies and smaller populations report similar survival outcomes for older and younger patients. However, the largest analysis (EBCTCG[33]) reported that patients in the 60 to 69 year age group with early breast cancer did not derive as much survival benefit as younger patients.

In terms of tolerability, three studies[31,32,34] reported information regarding dose intensity or treatment received. Where reported, results for older and younger patients were generally comparable.

None of the studies reported the use of QoL or CGA.

Authors' conclusions generally suggest that chemotherapy is feasible and safe for older patients with breast cancer; however, older patients may be at risk of higher rates of AEs.

9 COMPARATIVE COHORTS

A total of three studies[52-54] compared two or more cohorts of patients and met the inclusion criteria for inclusion in the review. Study details are presented in Table 14.

9.1 Study characteristics

9.1.1 Overview

All three studies[52-54] were relatively small, recruiting 70, 71 and 73 patients, respectively. The studies were all single centre and were conducted between 1999 and 2005. Bajetta et al[52] and Hess et al[53] focussed on patients with advanced or metastatic breast cancer, whereas Hu et al[54] recruited patients with early breast cancer post-surgery. Ages of patients across the studies ranged from 55 to 89 years, and the majority of patients had a good PS score. Hess et al[53] compared capecitabine plus vinorelbine, and both Hu et al[54] and Bajetta et al[52] included oral capecitabine as comparators.

9.1.2 Early breast cancer

The study by Hu et al[54] was conducted in China and focussed on early breast cancer. The median age of patients was 64 and 61 years, respectively, across the study arms. Performance status was measured using KPS.

9.1.3 Advanced or metastatic breast cancer

Two studies[52,53] focussed on advanced or metastatic breast cancer.

Table 14 Study characteristics, comparative cohorts

Study	Study details	Population	Intervention (N)	Baseline data	Outcomes	Author conclusions
Early breast cancer						
Hu 2010[54]	Single centre China 2002-2005	Stage IIa Post-surgery 55-69 years	Oral capecitabine monotherapy 2000 mg/m^2 (n=34)	Mean age: 64 years ± 4.13 KPS (SD): 89±0.23	Primary: OS Secondary: QoL, safety	Capecitabine monotherapy is a potential alternative to FEC adjuvant chemotherapy in patents ≥55 years with stage IIA breast cancer
			FEC 600 mg/m^2;75 mg/m$^{2;}$ 500 mg/m^2 (n=37)	Median age: 61 years ± 2.57 KPS (SD):93±0.15		
Advanced or metastatic breast cancer						
Bajetta 2005[52]	Phase II-sequential Single centre Italy 1999-2003	Metastatic breast cancer ≥ 65 years	Capecitabine (oral) (n=30) 65-69=6 (20%) 70-79=19 (63%) >80=5 (17%)	Median age: 73 years (65-89) ECOG PS: ≥2=0	Primary: Toxicity, TTP	Capecitabine is safe and effective in elderly breast cancer patients
			Capecitabine (oral) (n=43) 65-69 years=11 (26%) 70-79 years=31 (72%) >80=1 (2%)	Median age: 73 years (65-89) ECOG PS: ≥2=1/43 (2%)		
Hess 2007[53]	Single centre Switzerland 2001-2005	Metastatic or locally advanced breast cancer ≥ 65 years	Capecitabine 1000 mg/m^2 Vinorelbine 20 mg/ m^2 (n=23)	Median age: 75 years (66-83) WHO≥2: 3 (13%)	Primary: Toxicity Secondary: TTP, ORR	Response rates were comparable to published results, lower capecitabine doses were appropriate
			Capecitabine 1250 mg/m^2 Vinorelbine 20 mg/m^2 (n=47)	Median age: 72 years (64-85) WHO ≥2: 11 (23%)		

FEC=cyclophosphamide, epirubicin and 5-fluorouracil; KPS=Karnofsky performance status; SD=standard deviation; ECOG PS=Eastern Cooperative Oncology Group performance status; WHO=world Health Organisation; TTP=time to progression; ORR=overall response rate; OS=overall survival

9.2 Efficacy evidence

Three cohorts reported survival outcomes,[52-54] all of which included capecitabine therapy alone[52,54] or in combination with vinorelbine.[53] Studies are summarised in Table 15.

9.2.1 Early breast cancer

Hu et al[54] reported 3-year OS rates of 96.97% for oral capecitabine and 96.67% for FEC. No other efficacy outcomes were reported.

9.2.2 Advanced or metastatic breast cancer

Two studies reported outcomes for standard doses of capecitabine compared with a reduced dose.[52,53] Bajetta et al[52] demonstrated a longer, though not significantly greater, TTP for the lower starting dose of capecitabine compared with the standard starting dose (4.1 vs 3.9 months). Hess et al[53] also demonstrated nonsignificant increase in TTP for the lower starting dose. TTP was longer with the combination of capecitabine plus vinorelbine[53] compared with capecitabine monotherapy.[52]

Table 15 Efficacy evidence, comparative cohorts

Study	Intervention	Median PFS/TTP (95% CI) Months	Hazard ratio (95% CI)	Survival data	Hazard ratio (95% CI)	ORR (95% CI) %	Hazard ratio (95% CI)
Early breast cancer							
Hu 2010[54]	Oral capecitabine monotherapy	NR	NR	3-year OS rate: 96.97% 5-year OS rate: 93.33%	NR	44.7 (28.6 to 61.7)	NR
	FEC	NR	NR	3-year OS rate: 96.67% 5-year OS rate: 90.32%	NR	50 (35.2 to 64.8)	NR
Advanced or metastatic breast cancer							
Bajetta 2005[52]	Capecitabine-standard starting dose of 1250 mg/m^2	TTP: 3.9	NR	NR	NR	36.7 (19.9 to 56.1)	NR
	Capecitabine-low starting dose of 1000 mg/m^2	TTP: 4.1	NR	NR	NR	34.9 (21.0 to 50.9)	NR
Hess 2007[53]	Capecitabine 1000 mg/m^2 Vinorelbine 20 mg/ m^2	TTP: 7.0 (4.1 to 8.3)	NR	NR	NR	NR	NR
	Capecitabine 1250 mg/m^2 Vinorelbine 20 mg/ m^2	TTP: 4.3 (3.5 to 6.0)	NR	NR	NR	NR	NR

CEF=cyclophosphamide, epirubicin and 5-fluorouracil; TTP=time to progression; NR=not reported; OS=overall survival; ORR=overall response rate; CI=confidence interval

9.3 Tolerability evidence

9.3.1 Early breast cancer

Hu et al[54] reported that all patients in the capecitabine arm received the full six cycles, and that 84% of patients in the CEF arm received six cycles.

9.3.2 Advanced or metastatic breast cancer

Two studies[52,53] presented data regarding tolerability. Bajetta et al[52] reported that 91% and 98% of patients in both capecitabine arms, respectively, received the planned dose intensity. Discontinuations and dose reductions were common across studies, and grade 3-4 AEs were less common in patients aged <70 years.[52] There were two toxic deaths reported in Bajetta et al.[52] Hess et al[53] compared patients with and without bone metastases, and found that patients with bone metastases had much higher rate of discontinuation and rates of neutropenia (13% vs 35%).

Table 16 Tolerability evidence, comparative 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
Early breast cancer				
Hu 2010[54]	Capecitabine All patients received the planned 6 cycles	NR	NR	Hand-foot syndrome 3 (9%)
	CEF received: 6 cycles=84% 4 cycles=11% 2 cycles=5%	Discontinued: n=6/37 (16%)	Dose of epirubicin reduced after 1-2 cycles to 80-90% due to adverse reactions	Overall=13/37 (35%) GI=7/37 (19%) Neutropenia=4/37(11%)
Advanced or metastatic breast cancer				
Bajetta 2005[52]	Capecitabine 1250 mg/m2 91% of the planned dose intensity Median cycles (range): 6 (1-8)	Discontinued due to grade 3 diarrhoea=2/30 Discontinuation due to AE=2 (7%)	Dose reduction (50-75%) 18% of administrations in 30% of patients More likely in patients with impaired renal function	Total n=11 (37%) Toxic death=2 (7%) Diarrhoea=4 (13%) AEs more likely in patients with renal impairment
	Capecitabine 1000 mg/m2 98% of the planned dose intensity Median cycles (range): 6 (1-8)	Discontinued due to AMI, heart failure, or grade 4 diarrhoea=3/43	3% of administrations in 2% of patients	Total n=12 (28%) Fatigue n=5 (12%) Events less likely in patients <70 years Grade 3-4<70=10% Grade 3-4 >70=32%
Hess 2007[53]	Patients with bone metastasis Median dose intensities n=216 cycles Capecitabine 977.7 mg/m2 Vinorelbine 19.3 mg/m2	NR	Capecitabine: Dose reduction in 23% Vinorelbine: Dose reduction 14% Omitted 4.5%	Neutropenia=8/23 (35%)
	Patients without bone metastasis Median dose intensities n=216 cycles Capecitabine 1208.7 mg/m2 Vinorelbine 18.9 mg/m2	NR	Capecitabine: Dose reduction in 12% Vinorelbine: Dose reduction 4.6% Omitted 2.3%	Neutropenia=6/47(13%)

FEC=cyclophosphamide/epirubicin/5-fluorouracil; NR=not reported; GI=gastrointestinal; AMI=acute myocardial infarction; AE=adverse event

9.4 Comprehensive geriatric assessment and quality of life

One study[53] which focussed on advanced breast cancer presented QoL data. Eleven different measures were used in the study, and there were no statistically significant changes in QoL over time. Summary data are presented in Table 17; detailed results are presented in Appendices 4 and 5.

Table 17 Comprehensive geriatric assessment and quality of life, comparative cohorts

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
Advanced or metastatic breast cancer				
Hess 2007[53]	NR	NR	11 linear analogue self-assessment indicators	No substantial changes were observed across time points vs baseline

NR=not reported

9.5 Discussion

The included comparative cohorts were small studies, and all compared capecitabine-containing regimens.

No statistically significant efficacy results were presented. Tolerability outcomes were recorded by all three studies;[52-54] however, results are difficult to compare because of the differences in measures used.

Only one study[53] presented data on QoL, and there were no data regarding the use of CGA.

The authors' conclusions suggest that capecitabine-containing regimens are safe and tolerable in older patients with breast cancer.

10 SINGLE COHORTS

10.1 Study characteristics

Thirty-one prospective single cohorts met the inclusion criteria and were included in the review.[55-85] Study details are presented in Table 18.

10.1.1 Overview

The studies were conducted between 1993 and 2011. Sixteen of the studies were multicentre,[58,62,63,67-72,74,78-81,84,85] and none of the studies were international. The cohort sizes ranged from 10 to 2027. The definition of 'older' ranged from aged ≥55 to ≥70 years. The PS was reported in 24 studies.[55-58,60,62-72,74,76,79-83,85] In these single-cohort studies, there was a trend for including higher proportions of ECOG PS ≥2 patients than in the RCTs or subgroup analyses included in this review, with the highest proportion being 32% as reported in Dinota et al.[64] Thirteen studies included first-line chemotherapy regimens,[56-58,63,64,66-68,70,74,78,79,82] three included first- or second-line regimens,[62,65,77] and seven studies included adjuvant treatments.[59,73,75,76,81,84,85] Six studies compared older patients with a younger population.[58,61,68,80,81,84]

10.1.2 Early breast cancer

Eight studies focussed on patients with early breast cancer.[59,61,73,75,76,81,84,85] most studies were relatively small, ranging from 16 patients in the study by Wildiers et al[85] to 1224 patients in the study by Shayne et al.[81] Across the studies, patients generally had a good PS and median age was broadly similar.

Conclusions of the published studies generally suggest that chemotherapy for older people with breast cancer is well tolerated, and that age alone should not prevent older people from receiving chemotherapy.

10.1.3 Advanced or metastatic breast cancer

Twenty-three studies focussed on patients with advanced or metastatic breast cancer.[57,58,60,62-72,74,77-80,82,83] Most studies included less than 100 patients; the smallest study was by Gupta et al[71] with 10 patients, and the largest was the Biganzoli et al study[58] with 2027 patients.

Across studies, there was a higher proportion of patients with ECOG PS ≥2 or equivalent, and five studies[60,64,68,72,83] had more than 20% of patients with a higher PS.

Table 18 Study characteristics, single cohorts

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Early breast cancer: older vs younger patients						
Claire Dees 2000[61]	Single centre USA 1993-1996	Early breast cancer	Doxorubicin plus cyclophosphamide (n=44) ≥65=11 (25%)	Median age: <65=48.6 (35-62) ≥65=71.4 (65-79)	Toxicity	These data suggest that older age alone should not exclude patients from receiving adjuvant therapy with doxorubicin and cyclophosphamide
Watters 2003[84]	Multicentre Canada	Adjuvant chemotherapy	5-flourouracil, doxorubicin and cyclophosphamide (n=65)	Mean age: <65=55±6 (31-64) ≥65=70±5 (65-80)	QoL	Physical function and other functional domains are impaired in postmenopausal women during adjuvant chemotherapy for breast cancer, but recover subsequently. Physical function appeared to be better maintained in the older women, who tolerated adjuvant chemotherapy well overall. A knowledge of these effects is important for clinical decision-making and when defining social support needs during adjuvant chemotherapy
Shayne 2009[81]	Multicentre USA 2002-2005	Adjuvant chemotherapy Stage I-III Aged ≥65 years	All systemic chemotherapy ≥65=207 <65=1017	Median age: ≥65=70 (65-85) ECOG PS ≥65: 0=137 (66.2%) 1=61 (29.5%) 2-4=9 (4.3%)	Primary: Toxicity, tolerability	There were no significant differences noted with regard to chemotherapy related haematological toxicities between older and younger breast cancer patients in this large prospective observational study. This may be explained, in part, by more frequent reductions in RDI and less frequent utilisation of anthracyclines among older patients
Early breast cancer: older patients only						

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Kurtz 2000[75]	Phase I France	Adjuvant chemotherapy Early breast cancer ≥65 years	Idarubicin and cyclophosphamide (n=19) Level 1=3 Level 2=10 Level 3=6	Median age: 71 (66-76)	Toxicity	The toxicity of an oral combination of escalated doses of idarubicin plus cyclophosphamide was acceptable in early breast cancer patients
Hurria 2006[73]	USA 2001-2003 Follow-up completed Dec 2004	Adjuvant chemotherapy Stage I-III Aged ≥65 years	CMF n=34 (69%) AC n=2 (4%) AC and paclitaxel n=12 (24%) AC-T and trastuzumab n=1 (2%)	Median age: 68 (65-84)	Primary: Toxicity	Despite toxicity from adjuvant chemotherapy, this cohort of relatively young older patients maintained their functional status and QoL from before chemotherapy to 6 months post chemotherapy. Subtle changes in higher-order functioning would require assessment using different geriatric assessment tools
Browall 2008[59]	Sweden 2003-2005	Adjuvant chemotherapy Stage I-III N=75 Aged ≥55 Older (65-77)=36/75 Younger (55-64)=39/75	FEC (n=72) Or CMF (n=3)	Age range: 55-77	HRQoL	The results indicate that among postmenopausal patients in the age range 55-77 years consecutively selected for adjuvant chemotherapy age was not a predictor of decreased HRQoL. This supports the argument that age should not be used in isolation in decisions about adjuvant chemotherapy for breast cancer in elderly women
Wildiers 2008[85]	Multicentre Belgium Feb 2006-Sep 2006	Adjuvant chemotherapy Stage I-III Aged ≥65	PLD and cyclophosphamide (n=16)	Median age: 69 years (65-74) ECOG PS: 0=12 (75%) 1=1 (6%) Unknown=3 (19%)	Feasibility, toxicity	All but one patient finished the six planned cycles without major dose reductions or delay, and with limited serious toxicity showing the feasibility of this regimen

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Ladoire 2011[76]	France 2005-2009 Median follow-up=2 months	Adjuvant chemotherapy Aged >70 years	Epirubicin plus paclitaxel (n=59)	Median age: 74 years (70-86) WHO PS: 0=42 (71%) 1=17 (29%)	Primary: Toxicity	This study demonstrates the feasibility of weekly adjuvant chemotherapy including anthracyclines and taxanes in a sequential schedule. This regimen is safe in terms of hematologic, non-haematological, and cardiac toxicities, and showed encouraging efficacy, justifying further studies in geriatric patients
Advanced or metastatic breast cancer: older vs younger patients						
Perez 2002[80]	Phase II Multicentre USA Bristol-Myers Squibb	Metastatic breast cancer Aged ≥18 years	Paclitaxel (n=212) ≥65=73 (34%)	Median age: ≥65=73.5 (65.5 to 87.7) <60=54.8 (30.9 to 64.6) ECOG PS ≥65: 0=43% 1=44% 2=14%	Toxicity	Weekly paclitaxel therapy is a reasonable option for older patients with MBC
Freyer 2004[68]	Multicentre Phase II France Use of IPD 2000-2001	First-line chemotherapy Metastatic breast cancer Aged ≥70	Oral idarubicin (n=26)	Age: 70-74=9 (35%) 75-79=12 (46%) >80=5 (19%) ECOG PS≥2: 6 (23%)	Toxicity	Owing to the lack of efficacy and unacceptably high toxicity, weekly oral idarubicin should not be given to patients >70 years with poor PS and metastatic hormone-resistant breast cancer. The data obtained do not support the use of oral idarubicin in elderly patients, but oral administration of other drugs (vinorelbine, capecitabine) should be assessed, with careful monitoring of the patients, in light of our findings

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Biganzoli 2009[58] (abstract only)	Subpopulation analysis Multicentre	First-line chemotherapy Advanced breast cancer	Bevacizumab plus chemotherapy (n=2027) <65=1668 (82%) ≥65=359 (18%)	Median age: 54 years (21-93) ECOG PS ≥2: <65=4.9% ≥65=8.4%	Safety and efficacy	Treatment with bevacizumab is feasible in elderly patients. Hypertension was the only grade 3 bevacizumab -related side=effect reported more frequently in the older than in the younger cohort. Efficacy was similar in the two subgroups. These results suggest that the combination of bevacizumab with 1st-line chemotherapy shows a similar therapeutic index regardless of age
Advanced or metastatic breast cancer: older patients only						
Hainsworth 2001[72]	Multicentre Phase II USA 1997-1999	Advanced breast cancer Aged >65 or poor candidates for combination chemotherapy	Docetaxel (n=41)	Median age: 74 years (50-88) ECOG PS: ≥2=9 (22%)	Efficacy	Weekly docetaxel therapy is active and well tolerated by the elderly and/or poor-performance status patients with advanced breast cancer. Well-tolerated combination regimens containing weekly docetaxel merit evaluation for this patient population
Ten Tije 2004[82]	The Netherlands May 2003 Median follow-up=18.3 months (6.4- 37.5)	First-line chemotherapy Metastatic breast cancer	Paclitaxel (n=26)	Mean age: 77 years (71-84) WHO PS 0=4 (15%) 1=17 (65%) 2=5 (19%)	Primary: Toxicity Secondary: TTP	Weekly paclitaxel at this dose and schedule is an effective treatment regimen, and is feasible, but causes fatigue in a subset of patients

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Carola 2005 (abstract only)[60]	Single centre France Sanofi aventis	Metastatic breast cancer	Leucovorine, 5-fluorouracil, mitoxantrone (n=14)	Median age: 78 years (73–86) WHO PS: 2=28.6%	Survival without QoL decrease	These results reveal that specific screening for older patients are very hard to get from oncologists, and that if chemotherapy is probably possible for older people, many questions still remain especially regarding benefits/toxicity risks. More studies are needed to ensure that older cancer populations receive the most appropriate treatment
Del Mastro 2005[63]	Multicentre Italy 2000-2001	First-line Advanced breast cancer Aged ≥70 years	Paclitaxel (n=48)	Median age: 74 years (70-87) ECOG PS: ≥2=4 (8.37%)	Activity and toxicity	Weekly paclitaxel is highly active in elderly advanced breast cancer patients. Data on cardiovascular complications, however, indicate the need for a careful monitoring of cardiac function before and during chemotherapy
Dinota 2005[64]	Italy 2001-2003 Median follow-up=14 months	First-line chemotherapy Advanced breast cancer Aged >65 years	Gemcitabine plus vinorelbine (n=34)	Median age: 69 years (65-87) WHO PS: 0=5 (15%) 1=18 (53%) 2=11 (32%)	Primary: Toxicity, TTP, OS	The gemcitabine and vinorelbine combination shows significant activity in elderly metastatic breast cancer patients. The treatment is well tolerated and has an acceptable toxicity profile
Gupta 2005[71]	Multicentre Phase II USA 1999-2001	Advanced breast cancer Aged >65	UFT plus leucovorine (n=10)	Median age: 65.7 years (65-82) CALGB PS: 0-1=100%	Response rate, toxicity	Although UFT/leucovorin had efficacy in 1 patient, toxicity in the patients over 70 years of age was increased. Careful evaluation of anti-cancer drug toxicity in very elderly patients is important as our population ages

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Lorenzo 2005[77]	Spain	First- or second-line treatment Advanced breast cancer	Docetaxel (n=28)	Median age: 72 years (66–84)	Efficacy, safety	Docetaxel as a single agent is active in elderly patients with advanced breast cancer. The use of prophylactic G-CSF allowed the administration of high doses of docetaxel with minimal myelosuppression
Crivellari 2006[62]	Multicentre Phase II 2-part study Italy 1999-2004	First- or second-line chemotherapy Metastatic breast cancer Aged ≥65 years	Oral idarubicin (n=47) First part=14 Second part=33	Median age: First part of study 74 years (67-84) Second part of study 75 years (65-81) Median KPS: First part of study 90 (50-100) Second part of study 100 (60-100)	Primary: Toxicity Secondary : TTP, OS	This study shows that idarubicin at the dose of 5 mg/day for 21 consecutive days is feasible and effective in elderly breast cancer patients but does not demonstrate an improvement in efficacy. A determination of the idarubicin and darubicinol (IDOL) plasma levels (C_{trough}) is predictive for toxicity
Mattioli 2006 (abstract only)[78]	Phase II Multicentre Italy	First-line chemotherapy Metastatic breast cancer Aged >70 years	PLD (n=19)	Median age: 75 years (71-83)	Primary: RR Secondary: Toxicity	This study confirmed the liposomial doxorubicin as an active chemotherapy for MBC in elderly patients. Anyway, a particular attention is needed to prevent both allergic reactions as well as dermatological toxicity in elderly MBC patients treated with PLD
Basso 2007[57]	Phase II Italy 2002-2006	First-line chemotherapy Locally advanced or metastatic breast cancer Aged >70 years KPS ≥60	Vinorelbine plus gemcitabine (n=12)	Median age: 74 years (70-82)	Primary: Response, toxicity, QoL Secondary: TTP, OS	The promising response rates obtained with this combination by other authors could not be confirmed in our small cohort of older women with breast cancer, therefore the trial was prematurely terminated. We do not recommend the co-administration of gemcitabine to vinorelbine in women ≥70 years outside the setting of controlled clinical trials

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Kurtz 2007[74]	Phase II Multicentre France 2002-2005	First-line chemotherapy Metastatic breast cancer Aged 65-75 years	PLD-cyclophospamide (n=35)	Median age: 71.3 years (65.6-75.9) WHO PS: 0=12/35 1=23/35	Primary: RR Secondary: Tolerance, survival data	The PLD-cyclophosphamide combination is moderately active and safe in elderly metastatic breast cancer patients, but cannot be recommended routinely due to myelotoxicity and mucositis hazards
Addeo 2008[55]	Italy 2003-2004 Median follow-up 12 months	Metastatic breast cancer Aged ≥65 years	PLD plus vinorelbine (n=34)	Median age: 71 years (65-82) ECOG PS: >2=6 (9%)	Efficacy, toxicity	Our data suggest that this combination is active and well tolerated in elderly patients with MBC and could represent another efficacious chance for the management of this population
Girre 2008 (abstract only)[69]	Multicentre France 2005-2006	Metastatic breast cancer	Docetaxel (n=27)	Median age: 76 years (70-86) ECOG PS: 0-1=100%	IADL, PFS, OS	This study demonstrated once again that the elderly population is a very special population, in which any chemotherapy regimen should be carefully evaluated before its routine use
Mlineritsch 2009[79]	Multicentre Phase II Austria 2002-2004 Median follow-up 24 months	First-line Metastatic breast cancer Aged >60 years	PLD plus vinorelbine (n=42)	Median age: 68 years (60-82) ECOG PS ≥2=7 (17%)	Clinical activity, toxicity	The combination of PLD and vinorelbine is an active and well-tolerated regimen in elderly patients with MBC in first-line treatment
Addeo 2010[56]	Italy 2004-2007	First-line Aged ≥70 years	Vinorelbine (n=34)	Median age: 75 years (70-84) ECOG PS: ≥2=6 (18%)	Safety, activity	The fractionated administration of oral vinorelbine is well tolerated and presents promising activity in elderly patients with MBC, warranting further investigation in combination with other chemotherapy agents
Wang 2010[83]	Phase II China Jun 2001- Jul 2005 Median follow-up=14.6 months (5-49)	Advanced or metastatic breast cancer	Capecitabine plus weekly docetaxel (n=38) (41 for safety analysis)	Median age: 68 years (65-75) KPS: 60-70=16 (42%) 80-100=22 (58%)	Primary: TTP, OS Secondary: Toxicity	Capecitabine twice daily plus weekly docetaxel is active with an acceptably safety profile in Chinese women aged >65 years with MBC

Study	Study details	Population	Intervention, n	Baseline data	Outcomes	Author conclusions
Green 2011[70]	Phase IV Multicentre 5 Centres in Sweden 2007-2008 MSD, the Swedish Cancer Society, the Swedish Research Council	First-line chemotherapy Locally advanced or Metastatic breast cancer Aged ≥65 years	PLD (n=25)	Mean age: 72.3 years (65-81) WHO PS: 0=10 (40%) 1=13 (52%) 2=2 (8%)	Primary: TTP Secondary: Safety, response rate, TTP, OS	PLD is a safe and effective treatment for elderly breast cancer patients. Also potential predictive markers were identified
Falandry 2011 (abstract only)[66]		First-line Metastatic breast cancer Aged ≥70 years	PLD (n=60)	Median age: 77 years (70-88) ECOG PS: ≥2=15%	Tumour response	Despite manageable haematological toxicities and expected response rates, PLD tolerability was poor in light of non-haematological toxicities and geriatric outcomes
Foerster 2011 (abstract only)[67]	Multicentre Germany >2011	First-line Metastatic breast cancer	Bevacizumab plus paclitaxel (n=818)	≥65=32% ≥70=16% ECOG PS ≥2: 10%		First-line bevacizumab combined with paclitaxel in this elderly patient population offers a highly active and well-tolerated treatment, especially when considering that many of these patients may not be candidates for combination chemotherapy
Dong 2012[65]	Phase II China 2005-2009 Median follow-up=16.2 months	Mixed settings Metastatic breast cancer Aged ≥65 years	Gemcitabine plus vinorelbine (n=51)	Median age: 73 years (65-84) ECOG PS: 0=29 (56.9%) 1=17 (33.3%) 2=5 (9.8%)	Primary: Toxicity Secondary: PFS, OS	Gemcitabine in combination with vinorelbine is active and safe in elderly patients with anthracycline and taxane-pretreated MBC

RDI=relative dose intensity; CMF=cyclophosphamide, methotrexate and 5-fluorouracil; AC=doxorubicin plus cyclophosphamide; AC-T=doxorubicin, cyclophosphamide and paclitaxel; FEC=5-fluorouracil, epirubicin and cyclophosphamide; PLD=liposomal doxorubicin; ECOG PS=Eastern Cooperative Oncology Group performance status; WHO=World Health Organisation, CALGB=Cancer and Leukemia Group B; PS=performance status; QoL=quality of life; IPD=individual patient data; UFT=tegafur plus 5-fluorouracil; PLD=pegylated liposomal doxorubicin; MBC=metastatic breast cancer; G-CSF=granulocyte colony-stimulating factor; PFS=progression-free survival; OS=overall survival; RR=response rate; TTP=time to progression; HRQoL=health related quality of life; IADL=Instrumental Activities of Daily Living

10.2 Efficacy evidence

Evidence for efficacy outcomes is presented in Table 19.

10.2.1 Early breast cancer

None of the studies which focussed on early breast cancer reported efficacy outcomes of interest.

10.2.2 Advanced or metastatic breast cancer

Survival outcomes were reported in 18 studies.[55-58,62-67,69,70,74,77,79,80,82,83] Gemcitabine plus vinorelbine comparisons were analysed in two cohorts,[64,65] and the results for ORR were 33.3% in Dong et al[65] and 53% in Dinota et al.[64] Vinorelbine plus gemcitabine resulted in a significantly lower OS of 8.2 months.[57] PLD outcomes were reported in three studies[66,70,74] which showed similar median OS. PLD plus vinorelbine[55,79] had a decreased OS compared with PLD alone.[66,70] Two studies[69,77] reported significantly different ORRs for docetaxel.

Outcome data were presented in two studies that compared older patients with younger patients.[58,80] TTP and OS estimates for paclitaxel were found to be greater for patients older than 65 years of age compared to younger patients.[80] Bevacizumab plus chemotherapy was also slightly longer for the older population.[58]

Table 19 Efficacy outcomes, single cohorts

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)
Advanced or metastatic breast cancer							
Perez 2002[80]	Paclitaxel	TTP: ≥65=214 days <65=134	NR	≥65=377 days <65=429 days	NR	≥65=20 <65=22	NR
Biganzoli 2009[58]	Bevacizumab plus chemotherapy <65=1648 ≥65=352	TTP: <65=9.3 (9.0 to 9.8) TTP: ≥65=10.1 (9.4 to 11.3)	NR NR	NR	NR	<65=53.2 ≥65=46.4	NR
Ten Tije 2004[82]	Paclitaxel	TTP: 6.5	NR	NR	NR	NR	NR
Del Mastro 2005[63]	Paclitaxel	PFS: 9.7 (8.5 to18.7)	NR	NR	NR	53.7 (38.7 to 67.9)	NR
Dinota 2005[64]	Gemcitabine plus vinorelbine	NR	NR	NR	NR	53	NR
Lorenzo 2005[77]	Docetaxel	TTP: 10.7 (10 to11.5)	NR	26.6 (16.6 to 36.7)	NR	50 (32 to 69)	NR
Crivellari 2006[62]	Oral idarubicin	TTP: 3	NR	17*	NR	22 (9.6 to 41.1)	NR
Basso 2007[57]	Vinorelbine plus gemcitabine	TTP 3	NR	8.2	NR	NR	NR
Kurtz 2007 [74]	PLD-cyclophosphamide	PFS: 8.8 (6.6 to 11)	NR	20.3 (18.6 to 22)	NR	NR	NR
Addeo 2008[55]	PLD plus vinorelbine	TTP: 8 (6.7 to 8)	NR	13 (11.8 to 13.3)	NR	50 (36 to 66)	NR
Girre 2008 (abstract only)[69]	Docetaxel	NR	NR	NR	NR	27 (12 to 48)	NR
Mlineritsch 2009[79]	PLD plus vinorelbine	NR	NR	NR	NR	36	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)
Addeo 2010[56]	Vinorelbine	NR	NR	15.9 (13.1 to 15.91)	NR	38	NR
Wang 2010[83]	Capecitabine plus weekly docetaxel	TTP: 8.9 (2 to 34)	NR	17.6 (5 to 49)	NR	47	NR
Green 2011[70]	PLD	TTP: 5.7 (3.74 to 13.8)	NR	20.6 (6.58 to 25.6)	NR	NR	NR
Falandry 2011 (abstract only)[66]	PLD	PFS: 6.1	NR	15.7	NR	NR	NR
Foerster 2011 (abstract only)[67]	Bevacizumab plus paclitaxel	PFS: ≥65=9.2 ≥70=9.3	NR	NR	NR	57	NR
Dong 2012[65]	Gemcitabine plus vinorelbine	PFS: 6.2 (4.6 to 7.8)	NR	17.0 (14.5 to 19.5)	ECOG PS predictive factor: HR=2.4 (1.3 to4.7) p=0.007	33.3 (20.4 to 46.2)	NR

PLD=pegylated liposomal doxorubicin; PFS=progression-free survival; TTP=time to progression; CI=confidence interval; OS=overall survival; ORR=overall response rate; NR=not reported; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio

10.3 Tolerability evidence

Outcomes relating to tolerability are presented in Table 20.

10.3.1 Early breast cancer

Tolerability and adverse event data were provided in five[73,75,76,81,85] cohort studies that focussed on early breast cancer.

Hurria et al[73] reported that 18% and 20% of patients receiving CMF and anthracycline-based chemotherapy, respectively, received <85% of the planned RDI, and Shayne et al[81] reported an even higher figure of 34%. Where discontinuations were reported, the rates were low and primarily due to AEs.

In terms of AEs, Shayne et al[81] found that rates of febrile neutropenia, anaemia and thrombocytopenia were similar in old and young patients.

10.3.2 Advanced or metastatic breast cancer

Tolerability and AE data were reported by 23[55-58,60,62-72,74,77-80,82,83] studies. Three of these studies compared older and younger patients,[58,80,81] and did not find a significant difference in the number of AEs, dose delays or reductions between the two population groups.

Across the studies the proportion of patients who received all planned doses or cycles varied from 48%[66] to 81%.[72] Discontinuations were mainly due to toxicity and progression; one study[82] reported that 32% of patients discontinued treatment with paclitaxel due to fatigue.

The number of AEs was generally quite low, with a few exceptions: Freyer et al[68] reported that 35% of patients experienced serious AEs, Basso et al[57] reported grade 3 neutropenia in 25%, and Falandry et al[66] reported that of six study deaths, three were possibly related to treatment.

Table 20 Tolerability outcomes, 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
Early breast cancer				
Shayne 2009[81]	Planned RDI: ≥85%: ≥65=163 (78.8%) <65=873 (85.8%) <85%: ≥65=36 (17.4%) <65=125 (12.3%) (p=0.02) Unknown: ≥65=8 (3.9%) <65=125 (12.3%) Mean actual RDI was 85.6% overall (SD 17.6%) ≥65: 34% received an actual RDI <85% Planned and actual RDI differed with increasing age (p < 0.01).	NR	NR	Haematological toxicity: Febrile neutropenia: ≥65=92 (45.1%) <65=437 (43.7%) 60.6% of ≥65 receiving anthracyclines developed neutropenic complications compared with <65 (49.3%) (p=0.02) Anaemia: ≥65=56 (27.5%) <65=249 (24.9%) Thrombocytopenia: ≥65=22 (10.8%) <65=79 (7.9%)
Kurtz 2000[75]	Mean number of cycles: Level 1=5.3 Level 2=3.7 Level 3=4.2 Mean RDI: Level 1: IDA=71.8%, CPM=78.4% Level 2: IDA=86.2%, CPM=88.4% Level 3: IDA=55.6%, CPM=79.7% Patients achieving nine cycles=3 (one per level)	NR	NR	Cycles with Grade 3 neutropenia=20 (26%) Cycles with Grade 4 neutropenia=16 (20.8%) Grade 3 infection=5 (26.3%)
Hurria 2006[73]	Received <85% planned RDI: CMF: 18% Anthracycline based: 20%	Discontinued due to thrombotic complications=3 (9%)	At the doctors' discretion	Any grade 3-4: CMF=18 (53%) Anthracycline=8 (53%)

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
				CMF=18 (53%) Anthracycline=8 (53%) Haematological toxicity=13 (27%) CMF=12 (35%) Anthracycline=1 (7%) Non-haematological toxicity=15 (31%) CMF=7 (21%) Anthracycline=8 (53%)
Wildiers 2008[85]	PLD: Mean dose intensity=27.5 mg/m^2 Median dose intensity=27.7 mg/m^2 Cyclophosphamide: Mean dose intensity=462.5 mg/m^2 Median dose intensity=459.9 mg/m^2	Discontinuation=1 (6%) due to neutropenia and intolerance	Dose reductions=6 (37.5%) Dose delay of 1-5 weeks=8 (50%)	Grade 3 AEs: Neutropenia=3 (19%) Nausea=1 (6%) Fatigue=1 (6%) Hand-foot syndrome=2 (13%)
Ladoire 2011[76]	56 patients (95%) received 6 planned cycles of chemotherapy 54 patients (92%) received all 18 planned injections	3 patients stopped treatment prematurely: 1 patient after first cycle of paclitaxel presented with grade 3 neuropathy, and 2 after the first infusion of paclitaxel with grade 2 allergic reaction	NR	3 patients experienced grade 3 neutropenia
Advanced or metastatic breast cancer				
Perez 2002[80]	Median cycles: ≥65=4 (1-18) <65=4 (1-29) Average dose ≥65=76mg/m^2 <65=77mg/m^2	NR	Doses delayed/ decreased: ≥65=17% 9% due to toxicity, 8% for social reasons <65=13% 6% due to toxicity, 7% for social reasons	Grade 3 /4 neutropenia=15% in both groups Grade 3 neuropathy ≥65=12% <65=9%
Biganzoli 2009[58] (abstract)	NR	NR	NR	Grade ≥3: <65=48.2% ≥65=56.8% SAEs:

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
				<65=48.2% ≥65=56.8%
Hainsworth 2001[72]	Completed first course=32 (78%) Received all intended doses=26/32 (81%)	NR	NR	NR
ten Tije 2004[82]	Total cycles=101 Median delivered dose=240 mg/m^2 (210-270) Median number of cycles=4 (1-11) Patients completing at least 2 cycles=22 (84.6%) Patients completing 4 or more cycles=15 (57.7%) Patients continuing treatment after 4 cycles=9 (35%)	Discontinuation due to fatigue=8 (32%)	Patients with reduced cycles=2 One cycle=1 (4%) Two cycles=1 (4%) Dose escalation=6/23 (26%) Dose reduction=2/23 (8.7%)	Grade 3: Neutropenia=12% Anaemia=12% HSR=4% Fatigue=4% Neuropathy=4% Vomiting=4%
Freyer 2004[68]	NR	NR	NR	Three patients succumbed to toxic deaths, after 3, 3 and 5 weeks of treatment, respectively. Severe AEs=9/26 (35%)
Carola 2005[60] (abstract only)	NR	NR	NR	neutropenia grade 3–4=53%
Del Mastro 2005[63]	Number treated=46 Median administered cycles=6 (1-6) Received 6 cycles=24 (52.2%) Received 4+ cycles=35 (76.1%) Median delivered dose-intensity=56 mg/m^2/week (93% of planned dose intensity) 34 (73.9%) received at least 80% of the planned dose-intensity	NR	Interrupted=15 (32.6%), Due to progression=8 Due to toxicity=7	Toxic death=2
Dinota 2005[64]	Median cycles=4 (3-8) Median dose intensity: Gemcitabine=506 mg/m^2/week Vinorelbine=14 mg/m^2/week RDI:	NR	NR	WHO Grade 3-4 haematological toxicities: Neutropenia=7 (20%) Anemia=6 (17%) Thrombocytopenia=4 (11%) Non-haematological toxicities:

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
	Gemcitabine=0.87 Vinorelbine=0.84			Nausea/vomiting=9 (26%) Constipation=5 (14%)
Gupta 2005[71]	Total cycles=28 (median, 2.5; range, 1–7)	Two patients withdrew after the first cycle secondary to gastrointestinal toxicity and were not evaluated for response	A total of 9 cycles in 2 patients were administered at dose reductions (for grade 3 diarrhea and thrombocytopenia, respectively)	NR
Lorenzo 2005[77]	NR	NR	NR	Neutropenia (18% of patients and 5% of cycles). There was just one case of febrile neutropenia that resulted in toxic death.
Crivellari 2006[62]	Total cycles delivered: First part of study=34 Second part of study=132 Median cycles: First part of study=2 (1-6) Second part of study=3 (1-11) Median dose: First part of study=210 mg (105-630) Second part of study 315 mg (105-1165) First part of study: Patients not evaluable for response due to toxicity and patient refusal to continue treatment after first cycle=5 (35.7%)	NR	Treatment delays=14 (29.8%) Due to haematological toxicity=13 (27.7%) Due to non-haematological adverse event=1 (2.1%)	Toxic death due to grade 4 neutropenia and diarrhoea=1 (2.1%) Second part of study: Grade 3 neutropenia=1 (3%) Grade 4 neutropenia=1 (3%)
Mattioli 2006[78] (abstract)	Total of 88 courses 52.6% received planned 6 cycles	NR	NR	Major allergic reaction during the first infusion=2 (10.5%), G3–G4 dermatological toxicity=3 (16%)
Basso 2007[57]	Mean cycles=3.8 Average dose intensity: Vinorelbine=73% (26-100) Gemcitabine=74% (31-100)	Considering the minimum ORR of 11.1% and rate of absence of 'serious toxicity' of 75%, the trial was terminated	<75% of prefixed dose=20 (43.5%)	Grade 3 neutropenia=3 (25%) Grade 3 anaemia=1 (8.4%) Grade 3 gastrointestinal=2 (16.6%)

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
Kurtz 2007[74]	Total cycles=166 Median cycles=6 (1-9) Mean dose mg/m^2 PLD=37.8 (37.5-39.8) Cyclophosphamide=472 (446-498)	NR	NR	Number of grade 3 /4 events: Haematological=12 Non-haematological=5
Addeo 2008[55]	195 cycles delivered Median per patient=5 Median cumulative dose of PLD of 210 mg/m^2 (range 140–280) RDI=92%	NR	NR	NR
Girre 2008[69]	Total cycles=117 Median dose intensity/patient=90% (74-104) Cumulative dose intensity/patient=22.7% (18.5-25.9)	NR	Total cycles=117 Median dose intensity/patient=90% (74-104) Cumulative dose intensity/patient=22.7% (18.5-25.9)	NR
Mlineritsch 2009[79]	Total cycles=171 Median cycles per patient=4 Received 6 cycles=17 (40%) Received 5 cycles=2 (5%) Received 4 cycles=5 (12%) Received 3 cycles=8 (19%) Received 2 cycles=4 (10%) Received 1 cycle=6 (14%)	NR	NR	Neutropenia 18%
Addeo 2010[56]	Total cycles=184 Median cycles=5.4 Median treatment time=6 months Median dose intensity 70 mg/m^2 Median cumulative dose=840 mg/m^2	NR	NR	NR
Wang 2010[83]	Total cycles=157 Median number of cycles=4 (2-8) Patients completing at least 2 cycles=38	NR	Patients with treatment interruption for one month=1 (2%)	Grade 3 /4: Neutropenia=12% Alopecia=(7%) Nausea/vomiting=2% Nail toxicity=2%

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
Falandry 2011[66] (abstract)	48% completed 6 cycles	Discontinuation: Progression=18% Severe toxicities=22%, Death=10% Fracture=2%	15% of the patients needed dose reductions and 17% treatment delays ≥7 days	Hand-foot syndromes=14% Fatigue=22% Anorexia=9% Infection=19% Pain=17% Six patients died during treatment (3 possibly related to PLD)
Forester 2011[67] (abstract)	Mean duration of documented bevacizumab therapy was 7.0 months in patients <65 years and 6.4 months in patients ≥65 years	NR	NR	NR
Green 2011[70]	Median cycles=6 Mean cycles=7.4 (1-21)	Withdrawn from study due to non-measurable disease=3 (1 2%). Discontinuation due to PPE=2 (8%)	Dose reduction=10 (40%) Due to weight loss=6 (24%) PPE=4 (16%) Rash=1 (4%) Diarrhea=1 (4%)	Grade 3 Non-haematological toxicities: Diarrhea=1 (4%) Nausea=1 (4%) Vomiting=1 (4%) Fatigue=1 (4%) PPE=2 (8%) Rash=1 (4%) Infection=1 (4%) No grade 3-4 haematological toxicities noted. Four Serious AEs were possibly related to PLD
Dong 2012[65]	Total cycles=197 Median cycles=4 (1-6) Patients completed all cycles=20 (39.2%) 3 patients received one cycle of chemotherapy and were not evaluable due to follow-up loss, treatment-related nausea, and toxic death for gastrointestinal bleeding, respectively	Reasons for early treatment discontinuation: Withdrawal of consent=12 (23.5%) Complications or toxicity=10 (19.6%) Disease progression=8 (15.7%) Loss to follow-up=1 (2.0%)	Patients with reduction of drug dose to 75% starting dose=17 (33.3%) Due to haematological toxicity=15 (29.4%) Due to non-haematological toxicity=2 (3.9%) Patients requiring a second dose reduction (50% starting dose)=2 (3.9)	Treatment related nausea=1 (2.0%) Toxic death due to gastrointestinal bleeding=1 (2.0%) Grade 3 adverse events: Leukopenia=10 (19.6%) Neutropenia=11 (21.6%) Anaemia=7 (13.7%) Thrombocytopenia=5 (9.8%) Fatigue=3 (5.9%) Hepatotoxicity=1 (2.0%)

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
				Constipation=2 (3.9%) Neuropathy=2 (3.9%) Grade 4 adverse events: Leukopenia=4 (7.8%) Neutropenia=2 (3.9%) Hepatotoxicity=1 (2.0%)

RDI=relative dose intensity; SD=standard deviation; IDA=idarubicin; CPM=cyclophosphamide; PL-DOX=liposomal doxorubicin; NR=not reported; AE=adverse event; SAE=serious adverse event; WHO=World Health Organisation; PPE=palmar-plantar erythrodysesthesia

10.4 Comprehensive geriatric assessment and quality of life

Seven single-cohort studies[55,59,61,64,73,76,84] presented information relating to CGA or QoL. Table 21 summarises the studies and detailed results are presented in Appendices 4 and 5.

10.4.1 Early breast cancer

Comprehensive geriatric assessment

Hurria et al[73] used six CGA tools to measure outcomes, and Ladoire et al[76] used the IADL as a baseline measure.

Quality of life

Four studies[59,61,73,84] presented QoL data using five different tools. Two studies[73,84] concluded that although there was some decline in cognitive and physical function, patients recovered within 6 months of treatment. Two studies[59,61] found that age was unrelated to any decline in QoL.[59,61]

10.4.2 Advanced or metastatic breast cancer

Comprehensive geriatric assessment

None of the studies reported data relating to CGA.

Quality of life

Two studies[55,64] presented data relating to QoL. Both studies used the EORTC QLQ-C30, and one study[55] used the ADL and IADL in addition. Addeo et al[55] found that there was no significant change to QoL throughout the study, whereas Dinota et al[64] found that there were improvements in QoL after 4-6 cycles.

Table 21 Comprehensive 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
Early breast cancer				
Claire Dees 2000[61]	NR	NR	BCQ	We have not seen evidence of sizable differences in the decline of QoL in older patients compared with younger patients
Watters 2003[84]	NR	NR	EORTC QLQ-C30	Anthracycline-based adjuvant chemotherapy for breast cancer in postmenopausal women is accompanied by impairments in physical function and other functional domains that are mild to moderate in degree and recover by 6 months post-therapy
Hurria 2006[73]	ADL, IADL, GDS, Charlson Comorbidity Index, BMI, Mini-Mental State Examination	Pre, post and 6 month after chemotherapy	FACT-B	A subset of patients experienced a decline in cognitive function from before chemotherapy to 6 months after chemotherapy, and patients maintained their functional status and QoL from before chemotherapy to 6 months post-chemotherapy
Browall 2008[59]	NR	NR	EORTC QLQ-C30 EORTC-QLQ-BR23 HADS	Age was found to be unrelated to decreases in HRQoL and to the patterns of symptoms
Ladoire 2011[76]	IADL	As baseline measure	NR	NR
Advanced or metastatic breast cancer				
Dinota 2005[64]	NR	NR	EORTC QLQ-C30	A better QoL was obtained by a relevant percentage of patients after 4–6 cycles of chemotherapy
Addeo 2008[55]	NR	NR	EORTC QLQ-C30 IADL ADL	The evaluation of QoL did not show any significant change during the study

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life cancer questionnaire; EORTC-QLQ-BR23=European Organisation for Research and Treatment of Cancer quality of life breast cancer specific questionnaire; BCQ=Breast Cancer Chemotherapy Questionnaire, FACT-B=Functional Assessment of Cancer Therapy-breast; HADS=Hospital Anxiety and Depression Scale; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; GDS=Geriatric Depression Scale; HRQoL=health-related quality of life; NR=not reported

10.5 Discussion

The included single-cohort studies constitute a heterogeneous body of evidence, varying not only in size of study but also in the age of patients included and the chemotherapy regimens used. There was a trend for including slightly higher proportions of ECOG PS ≥2 patients than in the RCTs or subgroup analyses, although the majority of patients had good PS scores.

One study[75] of early breast cancer presented efficacy outcomes, but most of the studies focussed on QoL or safety outcomes rather than efficacy. Eighteen studies[55-58,62-67,69,70,74,77,79,80,82,83] of advanced or metastatic breast cancer reported efficacy outcomes. Three studies[58,80,81] compared older and younger patients, but there were no statistically significant differences in the results.

Twenty-eight[55-58,60,62-83,85] of the included studies presented data relating to tolerability, and where comparisons between older and younger patients were made there were no significant differences between the two groups in terms of dose delays or reductions.

Seven studies[55,59,61,64,73,76,84] reported on CGA or QoL. The QoL results suggest that chemotherapy may impair older patients but that this is reversed once treatment has finished.

The authors' conclusions generally suggested that chemotherapy is a safe and feasible treatment option for older people with breast cancer, and that age alone should not be the deciding factor when treatment decisions are made.

11 RETROSPECTIVE DATA

11.1 Study characteristics

Study characteristics for the retrospective studies are presented in Table 22.

11.1.1 Overview

The review included 20 retrospective studies. Sixteen studies[86-101] included data from older patients and four studies[102-105] compared older and younger patients. All studies were conducted between 1980 and 2010.

The data relating to older patients only consisted of four[90,95,99,100] multicentre studies, one of which involved 14 sites across France.[90] The largest study was Griffiths et al,[91] which included 610 patients. The smallest was Rossi et al[99] with 24 patients.

In studies comparing older and younger patients, three were single-centre studies[102,103,105] and one was a multicentre study.[104] The largest study contained 694 patients, but was presented in abstract form only.[102]

11.1.2 Early breast cancer

Eleven studies[87,90,92,93,96-98,100,101,103,105] focussed on early breast cancer. Two studies[103,105] compared older and younger patients, and nine studies[87,90,92,93,96-98,100,101] presented data on older patients only. The studies were relatively small, ranging from 14 patients to 263 patients, and studies used a number of treatment regimens, often mixing those treated with numerous different regimens into one cohort, for example O'Connor et al,[96] which included at least eight regimens.

The conclusions of the study authors suggested that the main barrier to tolerating chemotherapy in an older person is the risk of toxicity; however, a few studies[92,101] reported that the risk of toxicity was due to the choice of regimen and/or existence of comorbidities rather than chronological age'

11.1.3 Advanced or metastatic breast cancer

Nine studies[86,88,89,91,94,95,99,102,104] focussed on advanced or metastatic breast cancer. Two studies[102,104] presented data for older versus younger patients, and seven studies[86,88,89,91,94,95,99] presented data on older patients only. Data were often missing for study methods, age or PS. Three studies[86,91,104] investigated the use of trastuzumab, and many of the other studies investigated older treatment regimens.

The authors' conclusions generally suggest that chemotherapy is effective and well tolerated; certainly the two studies that compared older and younger patients suggest that all age ranges derived survival benefit, and that older people should be given the full dose of treatment.

Table 22 Study characteristics, retrospective data

Study	Study summary	Population	Intervention, n	Purpose	Authors conclusions
Early breast cancer: older vs younger patients					
Brunello 2005[103]	Single institution Greece Jan 1999-Dec 2003	Early breast cancer N=260 Median age: 74 years (70-97) ECOG PS: 0=47.7% 1-3=52.3% Control[a] n=260 Mean age: 61 years (50-59)	Intravenous CMF, reduced CMF or E-CMF (n=69) AC (n=5) MMM (n=8)	To review the characteristics of presentation of early BC in elderly women and to register the actual use of adjuvant chemotherapy at the institution in recent years	Elderly breast cancer patients receive much less adjuvant chemotherapy, according to each prognostic factor. N+ HR– disease probably represents the most reasonable indication. As the toxicity of the CMF regimen frequently caused interruption of treatment, alternative regimens should be assessed in this age class
Raza 2009[105]	Single centre Canada 2006-2007	Early breast cancer <65=86% >65=14%	AC-T, FEC-100 or FEC-D (n=263)	To analyse patients with early breast cancer treated with adjuvant chemotherapy consisting of FEC-100, AC-T cyclophosphamide, paclitaxel, or FEC-D and the incidence of febrile neutropenia in this patient population	Optimal chemotherapy RDI (>85%) for early breast cancer can be achieved at an academic cancer centre. This goal is less often accomplished in elderly patients, and thus a proactive approach is required for managing toxicity in this population
Early breast cancer: older patients only					
De Maio 2005[87]	Single centre 1991-2002	Adjuvant setting >60 and <65=100 (56%) >65=80 (44%) Median age: 64 years (60-73)	CMF (n=180)	To retrospectively review compliance and safety of adjuvant CMF in patients older than 60	In a highly selective population of patients aged >65, CMF is as feasible as in patients older than 60 and younger than 65 but with a relevant burden of toxicity
Hurria 2005[92]	USA 1980-2000	Adjuvant chemotherapy Stage I-III Mean age: 70 years (65-79) Mean age receiving:	CMF (n=66) Anthracycline-based regimen (n=66) AC	To assess patterns of toxicity and to determine impact of age, chemotherapy regimen and comorbid conditions on this toxicity	The risk of toxicity from adjuvant chemotherapy depended more on the type of regimen than the chronological age of the patient

Study	Study summary	Population	Intervention, n	Purpose	Authors conclusions
		CMF=71 (65-78) Mean age receiving: AC/AC-T=86.6 (65-79)	(n=22) AC-T (n=44)		
Oladipo 2006 (abstract only)[97]	Single centre UK 2003-2004	Adjuvant setting Median age: 64 years (60-74) ECOG 0-1=100%	AC, FEC, CMF or TAC (n=93)	To determine whether breast cancer patients aged ≥60 could be offered adjuvant chemotherapy safely while achieving an acceptable dose intensity of ≥85%	A high proportion of patients aged ≥60 achieved the intended dose intensity of ≥85% over this 2-year period with acceptable toxicity levels. This suggests that age alone should not disqualify patients from consideration of adjuvant chemotherapy
Zauderer 2009[101]	USA Oct 2002- Jun 2005 Dr Hurria's K23 AG026749-01 and Association of Speciality Professors- Junior Development Award in Geriatric Oncology.	Adjuvant or neoadjuvant chemotherapy Stage I-III Median age: 65 years	AC-T (n=162)	To examine the feasibility and toxicity of adjuvant dose dense chemotherapy in older women with breast cancer	The risk of toxicity depended more on comorbid medical conditions and baseline haemoglobin value than age
Freyer 2011[90]	Multicentre 14 sites in France Patient dossiers reviewed Dec 2009- April 2010 Part funded by Sanofi-Aventis France	Adjuvant chemotherapy All stages Median age: 73 years(70-85) Median KPS 100% (80-100) ECOG PS 0=30 (71%) 1=12 (29%)	Docetaxel plus cyclophosphamide (n=110)	To describe tolerance in women treated with adjuvant docetaxel plus cyclophosphamide chemotherapy in routine clinical care for breast cancer and the modalities of geriatric evaluations performed in routine practice	In a selected population of elderly patients, 4 cycles of adjuvant docetaxel plus cyclophosphamide is feasible without major toxicities
Sawaki 2012[100]	Multicentre Japan 2006-2009	Adjuvant setting Stages I-III Median age: 72.3 years (69-84)	Trastuzumab (n=39)	To evaluate the incidence of adverse events in an elderly population of HER-2-positive breast cancer patients treated with trastuzumab in an adjuvant setting	Elderly patients tolerated trastuzumab well, although careful management is needed

Study	Study summary	Population	Intervention, n	Purpose	Authors conclusions
O'Connor 2012[96]	Single centre USA 1997-2010	Adjuvant/ neoadjuvant chemotherapy Stage I-III Median age 70 (65-86) 65-69=47% 70-74=38% >75=15% ECOG PS 0-1=95%	All treatment (n=204) AC-T (54%) Docetaxel-cyclophosphamide (15%) AC (11%) CMF (8%) Single-agent taxane (4%) CAF (3%) Docetaxel-carboplatin (1%) Others (4%)	To examine the administration of adjuvant or neoadjuvant chemotherapy to older women with breast cancer treated at Roswell Park Cancer Institute	Successful administration of planned chemotherapy to older women with breast cancer was associated with improved OS. However, delivery of chemotherapy was associated with increased toxicity and reduced tolerance. Models allowing physicians to better risk-stratify older patients with breast cancer are needed and are under development
Oladipo 2012[98]	Single Centre UK 1999-2009	Adjuvant chemotherapy Median age: 69 years(65-78)	All treatment (n=101) AC (n=14) FEC 50 (n=4) FEC 60 (n=58) FEC 100 (n=15) CMF (n=6) FEC-D (n=2) E-CMF	The primary endpoint of the study was to determine the proportion of this group of patients who achieved the treatment RDI of ≥85%	A significant proportion of patients aged ≥65 achieved the intended dose intensity of ≥85% over this 10-year period, with manageable toxicity levels. This supports the use of these regimens as adjuvant chemotherapy for breast cancer in this age group

Study	Study summary	Population	Intervention, n	Purpose	Authors conclusions
			(n=2)		
Kaplan 2013[93]	USA 1990- 2010	Adjuvant chemotherapy Stage I-III Mean age: 80 years (75-94)	CMF, CAF, AC, CT, AC-T (n=74) Non-standard chemotherapy (n=14)	To assess adjuvant chemotherapy recommendations, administrations and disease specific survival for invasive breast cancer among patients ≥75 compared with younger women	Patients ≥75 recommended for adjuvant chemotherapy have a high rate of refusal and complications from therapy
Advanced or metastatic breast cancer: older vs younger patients					
Arce Salinas 2011 (abstract only)[102]	Single institution Mexico 2005-2008	Locally advanced or metastatic breast cancer >65 years (13.3%) <65 years (86.6%)	Neoadjuvant anthracyclines, taxanes or combination regimens (n=694)	To compare the association of dose intensity with complete pathological response (cPR) in older women	Breast cancer has the same presentation in younger and in older patients. Older patients receive less dose intense chemotherapy. This is associated with a reduced rate of cPR. Therefore, older patients should be treated with full doses taking into account the toxicity profile of the chemotherapeutic regimens as well as the physical and medical conditions of the patient
Kaufman 2012[104]	Multicentre USA Dec 2003-Feb 2006	First-line chemotherapy Median age: <65=50 (20-65) 65-74=69 (65-75) ≥75=79 (75-92) Metastatic breast cancer ECOG PS: 0-1: <65=361 (45.6%) 65-74=69 (47.9%) ≥75=25 (38.5%) 2+: <65=44 (5.6%) 65-74=11 (7.6%) ≥75=5 (7.7%)	Trastuzumab regimens: <65 (n=674) 65-74 (n=117) ≥75 (n=50) Non-trastuzumab regimens: <65 (n=118) 65-74 (n=27) ≥75 (n=15)	To examine elderly patients with HER2-positive MBC in terms of demographic, clinical characteristics, treatment patterns and safety and efficiency outcomes in the registHER observational study	Improved PFS across all age groups and similar trends for OS

Study	Study summary	Population	Intervention, n	Purpose	Authors conclusions
		Unknown: <65=387 (48.9%) 65-74=64 (44.4%) ≥75=35 (53.8%)			
Advanced or metastatic breast cancer: older patients only					
Rossi 2003 ELVIS trial[99]	Phase III Multicentre Italy Jan 1999- Dec 2000	First-line chemotherapy Advanced breast cancer Median age: 75 years (70-84) ECOG PS: 0=2 (8.3%) 1=18 (75%) 2=4 (16.6%)	Vinorelbine (n=24)	To retrospectively analyse data from elderly patients with advanced breast cancer treated with single-agent vinorelbine in accordance to the ELVIS schedule	Single-agent vinorelbine is active and well-tolerated in elderly patients with advanced breast cancer
Massacesi 2005[95]	Multicentre Italy 1999-2003	Metastatic breast cancer Median age: 70 years (66-82) ECOG PS ≥2: 5 (14%)	Docetaxel (weekly, bi-weekly, tri-weekly) (n=37)	The aim of this study was to evaluate the efficacy and toxicity profile of docetaxel administered under routine clinical conditions, at low dose intensity in heavily pre-treated patients affected by MBC	Docetaxel, even when administered at low dose-intensity, demonstrated good disease control and toxicity profile
Kotsori 2010[94]	Single Centre UK 2001-2008 Cridlan Fund	Locally advanced or metastatic breast cancer Median age: 74 years(69-93)	Capecitabine (full/reduced dose) (n=89)	The authors carried out a retrospective analysis from a prospectively maintained single-centre database of all patients aged ≥70 consecutively treated with single-agent capecitabine as 1st or 2nd/3rd line therapy in the Unit between 2001 and 2008	Capecitabine is an effective and well-tolerated drug in elderly patients with MBC including first- line treatment. Dose reduction is frequently required but does not appear to affect outcome
Davis 2011 (abstract only)[86]	SEER database 2000-2005	Metastatic breast cancer	Trastuzumab (n=345)	To assess predictors of survival in elderly metastatic breast cancer patients in the United States Medicare population	Hormonal status, greater nodal involvement, older age and increased co-morbidity burden were found to be significant predictors of death in elderly metastatic breast cancer patients

Study	Study summary	Population	Intervention, n	Purpose	Authors conclusions
Debled 2011[89]	Single centre France 2000-2007 F. Hoffmann- La Roche Ltd.	First-line chemotherapy Metastatic breast cancer Median age: 78.8 years (75–91.2) ECOG PS: 0-1=74 (63%) ≥2=43 (37%)	Capecitabine (n=67) Vinorelbine (n=31) Anthracycline (n=14) Docetaxel (n=5)	To describe the efficacy and tolerability of first-line monotherapy and combination chemotherapy regimens in patients ≥75 years of age treated during a period of 7 years	These results suggest that palliative chemotherapy should not be systematically excluded in this setting, but should be carefully discussed as it appears to be feasible with apparent benefit in selected patients
Griffiths 2011[91]	Single centre USA 200-2005 Gentech, Inc.	De novo stages I-IV Metastatic breast cancer Median age: 73 years	First-line trastuzumab (n=425) Delayed trastuzumab (n=185)	The objectives of this study were to describe patterns of infused therapy in a cohort of older women who first received trastuzumab following diagnosis of MBC, and to identify factors associated with longer survival	Adding chemotherapy to first-line trastuzumab for MBC is associated with improved cancer survival
De Sanctis 2012[88]	Single centre Italy 2002-2009	First-line chemotherapy Metastatic breast cancer Median age: 76 years(65-88) ECOG PS: 2=11 (14.7%)	Capecitabine (n=75)	To evaluate the efficacy and safety of capecitabine and its impact on QoL in elderly patients aged ≥65 diagnosed with MBC	The results indicate that capecitabine is active and well tolerated in elderly patients with MBC. This dosing regimen warrants further study in the first-line setting for patients with less aggressive MBC who are not candidates for combination therapy

[a] Control group=equal cohort of younger randomly selected postmenopausal patients

AC=doxorubicin/cyclophosphamide; AC-T=doxorubicin/cyclophosphamide/paclitaxel; CMF=cyclophosphamide/methotrexate/fluorouracil; CAF=cyclophosphamide/doxorubicin/fluorouracil; FEC-100=fluorouracil/epirubicin/cyclophosphamide;FECD=fluorouracil/epirubicin/cyclophosphamide,/docetaxel;E-CMF=epirubicin/CMF; MMM=methotrexate/mitoxanthrone/mitomycin C; TAC=docetaxel/doxorubicin/cyclophosphamide; AC-T=doxorubicin, cyclophosphamide and paclitaxel; RDI=relative dose intensity; PFS=progression-free survival; OS=overall survival; QoL=quality of life; MBC=metastatic breast cancer; KPS=Karnofsky performance status; ECOG PS=Eastern Cooperative Oncology Group performance status

11.2 Efficacy evidence

Details of the efficacy outcomes are presented in Table 23.

11.2.1 Early breast cancer

Brunello et al[103] assessed the efficacy of five different chemotherapy regimens. The OS was not reported by regimen, but the 2-year OS for chemotherapy was 92.5% (95% CI 88.9% to 96.1%).

11.2.2 Advanced or metastatic breast cancer

Six studies[86,88,89,94,95,99] reported survival outcomes. Three studies[88,89,94] reported outcomes for capecitabine, one of which compared full-dose capecitabine with a reduced dose.[94] In this study TTP was not significantly different between the two regimens (p=0.5). The OS was also similar, at 72 months for the full-dose regimen and 61 months for the reduced dose.

Two studies[89,95] reported outcomes for docetaxel, with a relatively high OS of 27.4 months [89] and a lower OS of 16 months.[95] Two studies[89,99] reported similar outcomes for vinorelbine.

Table 23 Efficacy outcomes, retrospective data

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)
Early breast cancer							
Brunello 2005[103]	Intravenous CMF Reduced CMF AC E-CMF MMM	NR	NR	2 year OS=92.5% (88.9 to 96.1)	NR	NR	NR
Advanced or mtastatic breast cancer							
Rossi 2003[99]	Vinorelbine	PFS: 5 (range, 2-40+)	NR	11 (range 3-40+)	NR	NR	NR
Massacesi 2005[95]	Docetaxel	NR	NR	16 months (range 2-48)	NR	24% (10% to 39%)	NR
Kotsori 2010[94]	Capecitabine (treated with full dose)	TTP: 27 (12 to 43)	NR	72 (37 to 103)	NR	48%	NR
	Capecitabine (treated with reduced dose)	TTP 30 (28 to 32) p=0.5	NR	61 (53 to 68)	NR	42% (p=0.9)	NR
Davis 2011[86] (abstract)	Herceptin	NR	NR	Mean OS 2.6 years	NR	NR	NR
De Sanctis 2012[88]	Capecitabine	TTP: 9 (7 to 9)	NR	24 (21.7 to 24)	NR	24%	NR
Debled 2011[89]	Overall population	PFS: 6.2 months (4.1 to 8.1)	NR	13.8 (11.4 to 16.3) Age: 75-76=14.1 (12.5 to 15.8) 77-79=9.0 (3.6 to 14.4) ≥ 80=14.6 (9.5 to 19.6)	NR	NR	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)
	Capecitabine	8.1 (5.2 to 11.0)	NR	17.1 (12.4 to 21.8)	NR	NR	NR
	Vinorelbine	5.1 (0.9 to 9.2)	NR	9.9 (4.7 to15.1)	NR	NR	NR
	Anthracycline	5.8 (1.8 to 10.0)	NR	9.5 (1.1 to 17.9)	NR	NR	NR
	Doxetaxel	5.1 (1.6 to 8.6)	NR	27.4 (0.0 to 73.8)	NR	NR	NR

AC=doxorubicin/cyclophosphamide; CMF=cyclophosphamide/methotrexate/flouracil; E-CMF=epirubicin/CMF; MMM=methotrexate/mitoxanthrone/mitomycin C; PFS=progression-free survival; TTP=time to progression; OS=overall survival; ORR=overall response rate; NR=not reported

11.3 Tolerability evidence

Evidence relating to tolerability is presented in Table 24.

11.3.1 Early breast cancer

Ten studies[87,92,93,96-98,100,101,103,105] presented information on tolerability. Brunello et al[103] reported that 73.1% of patients received the planned cycles, and Raza et al[105] and Oladipo et al[97] reported that 64.8% and 91.4% received >85% of the planned RDI, respectively. De Maio et al[87] reported that 76% of patients aged over 65 received all planned cycles, and Hurria et al[92] reported that all patients received at least four cycles.

Brunello et al[103] reported that early interruptions were statistically significantly higher in patients aged over 70 ($p<0.0001$).

11.3.2 Advanced or metastatic breast cancer

Six studies[88,89,94,95,99,102] presented data on tolerability. Many chemotherapy regimens required dose delays or dose reductions, with the exception of Rossi et al,[99] which reported no omissions or postponements of treatment. Arce Salinas et al[102] found that dose reductions among those aged over 65 were statistically significantly higher than among those aged less than 65 ($p=0.00001$).

Table 24 Tolerability outcomes, retrospective data

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
Early breast cancer				
Brunello 2005[103]	Patients completed planned number of cycles=60 (73.1%)	Discontinuations=22 (26.8%)	>70 vs <70 Early interruption: 25.9% vs 4.7% *p*<0.0001 Dose reduction >25%: 5.2% vs 5.9% p=0.8105 Delay ≥2 weeks: 5.2% vs 11.9% p=0.1327	>70 vs <70 Grade 3-4 haematological: 22.1% vs 15.4% p=0.2821 Grades3-4 non-haematological: 3.9% vs 1.2% p=0.2831
Raza 2009[105]	RDI >85%=64.8% (<65=93.3)	NR	Dose delay >7 days=10.8% (<65=15%) Dose reduction=54% (<65=16.8%)	NR
De Maio 2005[87]	Received 6 cycles: >60 and <65=81 (81%) >65=61 (76%) Low compliance >60 and <65=39 (39%) >65=46 (58%) Actual/panned duration ≤1.25: >60 and <65=99 (99%) >65=78 (98%)	Treatment discontinuation due to: Protocol completion >60 and <65=81 (81%) >65=61 (76%) Patient refusal >60 and <65=6 (6%) >65=9 (11%) Treatment toxicity >60 and <65=11 (11%) >65=7 (9%) Other >60 and <65=2 (2%) >65=3 (4%)	No. of patients with modified dose due to toxicity >60 and <65=5 >65=2 Rate of cycles at reduced dose ≤25%: >60 and <65=86 (86%) >65=66 (82%)	Grade 3-4 toxicity >60 and <65=38% >65=39% p=1.00
Hurria 2005[92]	All patients received at least 4 cycles.	CMF patients who did not receive the planned 8 cycles=5 (8%) AC patients who did not receive the planned 8 cycles=1 (5%)	CMF dose reductions=6 (9%) Due to concern about toxicity=3 (4.5%) Due to toxicity=3 (4.5%)	Grade 3 or 4 haematological toxicities: CMF=18% AC=32% T of AC-T=2%

		AC-T abbreviated therapy due to toxicity=5 (11%)	AC dose reductions=3 (14%) Due to concern about toxicity=2 (10%) Due to toxicity=1 (5%) AC-T dose reductions due to toxicity=7 (16%)	Grade 3 or 4 non-haematological toxicities: CMF=14% AC=17% T of AC=20%
Oladipo 2006[97] (abstract only)	Dose intensity ≥85%=91.4%	NR	NR	Grade 3-4 non-haematological toxicity=13.9%
Zauderer 2009[101]	NR	Patients who did not complete the planned 8 cycles: AC portion=10 (6%) Taxane portion=26 (16%) due to patient preference=5% Allergic reaction=3% Grade 3 neutropenic fever=2% Grade 3 fatigue=2% Treatment discontinuation: <70=23 (19%) ≥70=13 (33%)	Patients requiring dose reductions=12 (7%) <70=7 (6%) ≥70=5 (13%) During AC portion=10 (6%) During taxane portion=2 (1%) Dose delay: <70=57 (46%) ≥70=24 (62%) Patients switched from paclitaxel to docetaxel=8 (5%) most often for allergic reaction	Grade 3 or 4 toxicity=67 (41%) <70=50 (41%) ≥70=17 (44%) Haematological toxicity=27 (17%) <70=20 (16%) ≥70=7 (18%) Non-haematological toxicity=59 (36%) <70=44 (36%) ≥70=15 (39%) Treatment-related mortality=1 (secondary to Grade 5 pneumonitis).
Sawaki 2012[100]	NR	Discontinuation due to toxicity: 3/39 (7.7%) Interrupted treatment due to toxicity: 1/39 (2.6%)	NR	NR
O'Connor 2012[96]	RDI<85%: Overall=41 (20%) 65-69=11 (27%) 70-74=20 (49%) ≥75=10 (24%) Incomplete treatment: Overall=41 (20%) 65-69=12 (29%) 70-74=19 (46%) ≥75=10 (24%)		Dose delay: Overall=41 (20%) 65-69=15 (37%) 70-74=19 (46%) ≥75=7 (17%) Dose reduction: Overall=19 (9%) 65-69=8 (42%)	

			70-74=9 (47%) ≥75=2 (11%)	
Oladipo 2012[98]	101 patients (78.2%) achieved planned RDI Received at least 85% RDI 65-69=81.3% >70=67.6%; p=0.09	NR	NR	NR
Kaplan 2013[93]	Completion rate: Standard chemotherapy=55 (81%) Non-standard chemotherapy=69% Switched to non-standard=28% 65-69=223 (91%) 70-74=106 (83.5%) ≥75=64 (72.7%) *P* <0.001 Therapy completion: CMF=23 (61%) AC-T, AT or CAF-T=20 (90%), AC or CAF=8 (100%) CT=11 (100%) Carboplatin plus taxane=6 (67%) Non-standard regimen=13 (69%)	NR	NR	NR
Advanced or metastatic breast cancer				
Arce Salinas 2011 (abstract only)[102]	Overall optimal dose intensity=80% of planned dose Taxane therapy dose intensity less than standard: <65=8.8% >65=17.6% p=0.03	NR	Anthracycline therapy dose reduction: <65=2.1% >65=27.8% p=0.00001	NR
Rossi 2003[99]	Median number of cycles=5 (2-6)	NR	No cycles were omitted or postponed.	Haematological toxicities: Grade 3 neutropenia=5 (20.8%) Grade 4 neutropenia=1 (4.1%) Non-haematological toxicities: Grade 3 constipation=1 (4.1%) No toxic deaths.
Massacesi 2005[95]	Overall=21 mg/m^2 (range 11-32) Median weekly dose intensity=20 mg/m^2 (range 12-31)	Withdrawal=16% Discontinuation due to adverse events=5%	NR	NR

	Median overall cumulative dose=320 mg/m^2 (31-700).			
	Docetaxel: Bi-weekly Overall=21 mg/m^2 (range 11-32). Median weekly dose intensity=18 mg/m^2 (range 11-23). Median overall cumulative dose=320 mg/m^2 (31-700)	NR	NR	NR
Kotsori 2010[94]	NR	NR	Dose reduction=53 (57%) Treatment delays=35%	NR
Debled 2011[89]	NR	Discontinuation due to: Progressive disease 72% Death 12% Adverse effects 7% Other 9%	NR	NR
	NR	Discontunuation due to: Progressive disease 55% Toxicity 16% Decreased global status 10% Other 10%	NR	NR
	NR	Discontinuations due to: Toxicity 36% Progressive disease 21% Other 21%	NR	NR
	NR	Discontinuations due to: Good response 2 patients Progressive disease 1 patient	NR	NR
De Sanctis 2012[88]	Compliant with therapy: 42/75 (56%)	NR	Dose reduction due to grade 3-4 AEs: 21/75 (28%)	Grade 3-4 hand-foot syndrome=6 (8%) Grade3-4 stomatitis=6 (8%)

RDI=relative dose intensity; CMF=cyclophosphamide/methotrexate/fluorouracil; AC=doxorubicin/cyclophosphamide; AC-T=doxorubicin, cyclophosphamide and paclitaxel; AE=adverse event; NR=not reported

11.4 Comprehensive geriatric assessment and quality of life

Quality of life was reported in only one retrospective study,[88] details of which are presented in Table 25.

Table 25 Comprehensive geriatric assessment and quality of life, retrospective data

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
De Sanctis 2012[88]	NR	NR	Clinical-benefit response as measure of increase in QoL	The QoL benefits in this population are encouraging

11.5 Discussion

Most of the included retrospective studies were relatively small, and many had missing data such as study details or methods, age and performance status. However, because much of the patient data in these studies was from registries or hospital databases and not from specifically selected populations, the data could be more reflective of routine clinical practice and therefore more useful to decision makers. Many studies investigated older chemotherapy regimens; however, a few used newer therapies, including trastuzumab.

Survival outcomes were reported in only seven studies, [86,88,89,94,95,99,103] with no comparisons between older and younger patients.

Fifteen studies[87-89,92-103,105] reported tolerability outcomes. In one study[103] where older and younger patients were compared, statistically significantly higher rates of treatment interruptions were seen in patients aged over 70, and another study[102] showed that dose reductions were statistically significantly higher in patients aged over 65.

There was a lack of QoL and CGA outcomes reported; however, this is to be expected as the studies analysed data retrospectively, and therefore the authors had no control over the original recording of data.

The authors' conclusions of the published studies suggest that chemotherapy is tolerated by older people with breast cancer, and that although there is a risk of toxicity, the regimen or patient comorbidities are likely to represent a higher risk than age itself.

12 OVERVIEW OF THE EVIDENCE

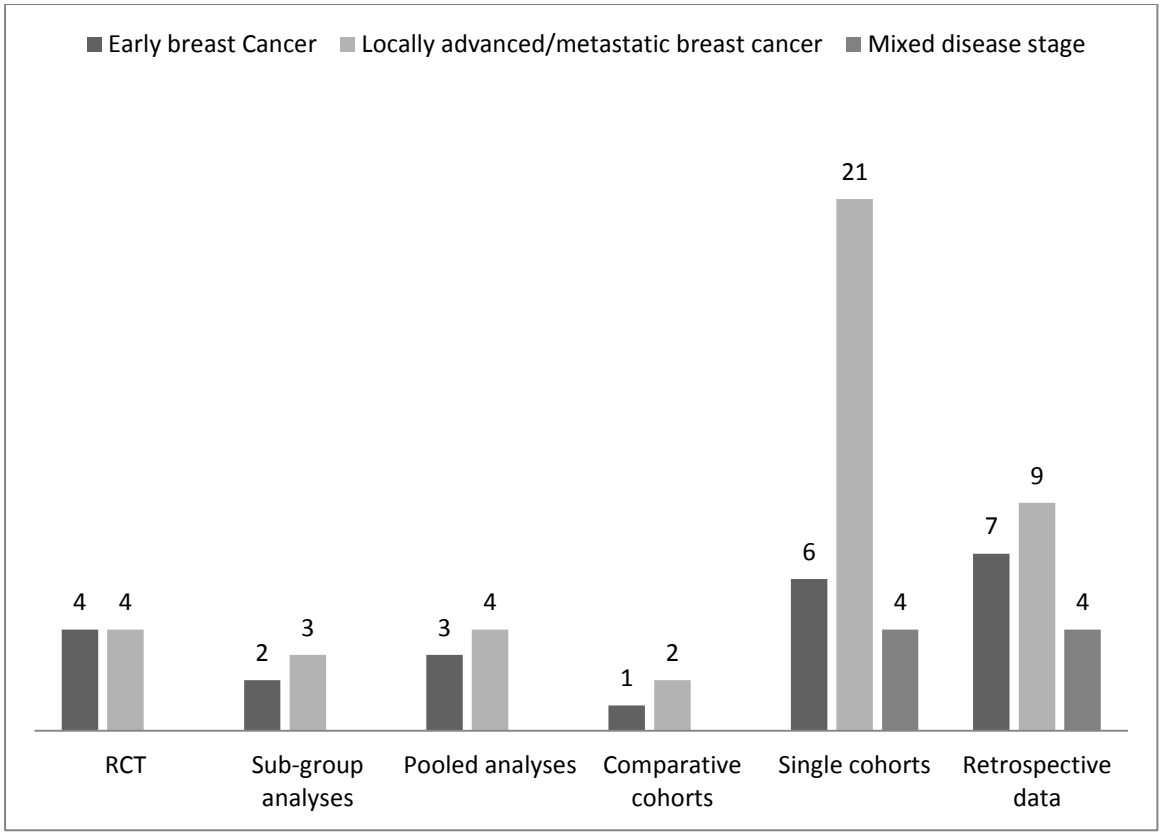
This section provides an overview of the available evidence and details:

- the varying chemotherapy regimens (Table 26)
- a breakdown of studies by disease stage (Figure 2)
- Brief overview of study characteristics (Table 27)
- summary of efficacy evidence for older versus younger patients (Table 28)
- summary of CGA and QoL tools used by included studies (Table 29)

Table 26: Chemotherapies used in studies

Bevacizumab plus chemotherapy	1 single cohort[58]
Bevacizumab plus paclitaxel	1 single cohort[67]
Capecitabine	3 trials[16,19,23] 1 pooled analysis[39] 2 comparative cohort[52,54] 3 retrospective studies[88,89,94]
Capecitabine plus docetaxel	1 single cohort[83]
Capecitabine plus Ixabepilone	1 pooled analysis[39]
Capecitabine plus vinorelbine	1 comparative cohort[53]
Cyclophosphamide, doxorubicin and 5-fluorouracil (CAF)	1 pooled analysis[38] 1 single cohort[84] 1 retrospective study[96]
Cyclophosphamide, epirubicin and 5-fluorouracil (FEC)	1 comparative cohort[54] 1 single cohort[59] 3 retrospective studies[97,98,105]
Cyclophosphamide, methotrexate and 5-fluorouracil (CMF)	3 trials[16,17,19] 2 single cohorts[59,73] 6 retrospective studies[87,92,96-98,103]
Cyclophosphamide, doxorubicin, and paclitaxel	1 pooled analysis[38]
Cyclophosphamide plus idarubicin	1 single cohort[75]
Docetaxel	1 trial[17] 2 subgroup[24,30] 3 single cohorts[69,72,77] 2 retrospective studies[89,95]
Docetaxel plus carboplatin	1 retrospective study[96]
Docetaxel plus cyclophosphamide	1 subgroup[25] 2 retrospective studies[90,96]
Docetaxel plus placebo	1 subgroup[28]
Docetaxel plus bevacizumab	1 subgroup[28]
Docetaxel plus doxorubicin and cyclophosphamide	1 pooled analysis[36]
Doxorubicin plus epirubicin and cyclophosphamide followed by docetaxel or paclitaxel	1 pooled analysis[36]
Doxorubicin plus docetaxel	1 pooled analysis[36]
Doxorubicin plus cyclophosphamide (AC)	2 trials[10,16] 1 subgroup[25] 2 single cohort[61,73] 5 retrospective studies[92,97O'Connor, 2012 #23,98,103]

Doxorubicin plus cyclophosphamide with or without paclitaxel	1 pooled analysis[38]
Doxorubicin plus cyclophosphamide and paclitaxel (AC-T)	1 single cohort[73] 4 retrospective studies[92,96,101,105]
Epirubicin	1 trial[12]
Epirubicin plus paclitaxel	1 subgroup[27] 1 pooled analysis[36] 1 single cohort[76]
Epirubicin and cyclophosphamide followed by CMF	1 subgroup[27]
Gemcitabine	1 trial[12]
Gemcitabine plus vinorelbine	1 trial[15] 3 single cohorts[57,64,65]
Gemcitabine plus mitoxantrone	1 trial[15]
Idarubicin	2 single cohorts[62,68]
Leucovorine, 5-fluorouracil, mitoxantrone	1 single cohort)[60]
Leucovorine plus UFT	1 single cohort[71]
Pegylated liposomal doxorubicin (PLD)	2 trials[10,23] 1 pooled analysis[32] 3 single cohorts[66,70,78]
PLD plus cyclophsophamide	2 single cohorts[74,85]
PLD plus vinorelbine	2 single cohorts[55,79]
No chemotherapy	1 trial[10]
Methotrexate, mitoxanthrone and mitomycin C (MMM)	1 retrospective study[103]
Paclitaxel	1 subgroup[24] 2 pooled analyses[31,34] 3 single cohorts[63,80,82]
Trastuzumab	3 retrospective studies[86,91,104]
Vinorelbine	1 single cohort[56] 2 retrospective studies[89,99]



RCT=randomised controlled trial

Figure 2 Breakdown of studies by disease stage

Table 27 Brief overview of study characteristics

• 48 studies included less than 100 patients • 26 studies included more than 100 patients
• 38 studies were multicentre • 36 studies were based in single centres
• 52 studies did not report funding source • 15 studies funded by pharmaceutical companies • 7 studies funded by research grants

Table 28 Summary of efficacy evidence, older versus younger patients

Study	Intervention	Median PFS/TTP (95%CI) Months	Hazard ratio (95%CI) P value	Median OS (95% CI) Months	Hazard ratio (95%CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
Pivot 2011[28]	Docetaxel+placebo	PFS: >65=7.6 ITT=8.1	>65: 15 mg/kg vs placebo 0.63 (0.383 to 1.032), p=0.07 ITT: 15 mg/kg vs placebo 0.67 (0.54 to 0.83) p<0.001	OS estimate 22.5	NR	44.7 (28.6 to 61.7	NR
	Docetaxel+bevacizumab (7.5 mg/kg)	PFS: >65=9 ITT=9		NR	NR	50 (35.2 to 64.8	NR
	Docetaxel+bevacizumab (15 mg/kg)	PFS: >65=10.3 ITT=10		OS estimate 25	NR	36.6 (22.1 to 53.1	NR
Biganzoli 2007[32]	PLD <70 years	PFS: 5.9 (5.4 to 8.3)	NR	NR	NR	NR	NR
	≥70 years	PFS: 5.6 (5.1 to 7.3)	NR	NR	NR	NR	NR
Vahdat 2011[39] (abstract only)	Ixabepilone plus capecitabine <65 vs ≥65 years	PFS: 5.6 vs 5.5	NR	14.7 vs 13.9	NR	42 vs 37	NR
	Capecitabine <65 vs ≥65 years	PFS: 4.2 vs 3.9	NR	13.0 vs 12.2	NR	26 vs 19	NR
Litchman 2012[34]	Paclitaxel <55 vs ≥65 years	NR	1.14 (0.96 to 1.35) p=0.31	NR	1.07 (0.90 to 1.27) p=0.73	NR	NR
	Paclitaxel 55 to 64 vs ≥65 years	NR	1.08 (0.90 to 1.30)	NR	1.04 (0.86 to 1.25)	NR	NR
Perez 2002[80]	Paclitaxel	TTP: ≥65=214 days <65=134	NR	≥65=377 days <65=429 days		≥65=20 <65=22	NR
Biganzoli 2009[58]	Bevacizumab plus chemotherapy <65=1648	TTP: 9.3 (9.0 to 9.8)	NR	NR	NR	53.2	NR

	Bevacizumab plus chemotherapy ≥65=352	TTP: 10.1 (9.4 to 11.3)	NR	NR	NR	46.4	NR
Foerster 2011 (abstract only)[67]	Bevacizumab plus paclitaxel	PFS: ≥65=9.2 ≥70=9.3	NR	NR	NR	57	NR

PFS=progression-free survival; TTP=time to disease progression; CI=confidence interval; ORR=overall response rate; ITT=intention to treat; NR=not reported

Table 29 Summary of CGA and QoL tools used

Comprehensive geriatric assessment tools	Quality of life measures
• Activities of Daily Living (ADL) • Instrumental ADL (IADL) • Vulnerable Elders Survey-13 (VES-13) • Charlson Comorbidity Index (CCI) • Geriatric Depression Scale (GDS) • Mini-Mental Status (MMS) • Karnofsky performance status (KPS) • Cumulative Illness Rating Scale for Geriatrics (CIRS-G) • Multidimensional Geriatric Assessment (MGA)	• Activities of Daily Living (ADL) • Instrumental ADL (IADL) • European Organisation for Research and Treatment of Cancer (EORTC) quality of life cancer questionnaire (QLQ-C30) • Hospital Anxiety and Depression Scale (HADS) • Linear Analogue Self-Assessment (LASA) • Physician-administered cognitive functioning • Vulnerable Elders Survey-13 (VES-13) • EORTC quality of life breast cancer specific questionnaire (QLQ-BR23) • Functional Assessment of Cancer Therapy-Breast (FACT-B) • Breast Cancer Chemotherapy Questionnaire (BCQ) • Clinical-benefit response as measure of increase in QoL

13 DISCUSSION

The World Health Organisation[6] 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[7] 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 recruited to breast cancer studies; the age of patients described as 'older' ranged from >55 years to >75 years across the included studies. The problem of defining patient populations is further complicated by the fact that definitions may vary depending on the life expectancy of patients with a specific disease; for example, a 50-year-old woman with breast cancer might be described as an older patient, whereas a 50-year-old man with lung cancer might be described as a younger patient. Only a limited number of studies were identified that reported exclusively on the treatment of older patients with breast cancer.

Data from the included RCTs are not generalisable to the older population, as strict selection processes would have ensured that the recruited patients were generally fitter and healthier than patients seen in routine clinical practice. However, data may be generalisable to the subgroup of older patients seen in routine clinical practice who are generally fit and healthy. None of the studies that reported data from RCT subgroups employed stratified randomisation by age, and therefore data from such studies must be interpreted with caution when assessing effectiveness because trial randomisation would not have been maintained in these subgroup analyses. Reports of combined analyses of IPD were limited by the authors' reliance on the available selective data. Data from the non-RCT studies included in the review were generally from single-centre studies that recruited potentially selected populations; indeed, the characteristics of the patient populations in the cohort studies indicate that patients were slightly more frail than those included in the RCTs, as the percentage of patients with an ECOG PS ≥2 was higher. Evidence from the retrospective studies may be more generalisable to the older population in general, as the patients included in these studies were not selected for fitness or comorbidity.

Taking all of this into consideration, this review presents evidence which shows that chemotherapy can be effective for older people with breast cancer. Comparisons across studies, regimens, measures and populations are difficult. However, there are data to suggest that chemotherapy does confer some survival benefit to older patients, and studies generally concluded that chemotherapy is a feasible treatment option for older people with breast cancer.

In terms of the tolerability of chemotherapy, it seems that older people can tolerate chemotherapy, although, for some patients, treatment comes with a higher risk of serious AEs in this age group compared with younger patients. The RDI measures generally showed that older patients can tolerate

the standard chemotherapy doses administered in the studies. However, treatment discontinuation rates and reductions in drug dosage were required more frequently in older patients, perhaps because they have a reduced ability to "bounce back quickly" after illness. In the studies that compared tolerability rates between older and younger patients, the discontinuation rates were generally higher in the older patients.

It was not the remit of the review to assess and compare efficacy evidence for the use of chemotherapy regimens in older patients; nonetheless, it proved difficult to provide a narrative summary of efficacy results due to the lack of data and to variability of the measures and outcomes reported. This was partly due to the fact that many studies focussed on measures of tolerability and safety.

The majority of studies reported comprehensive data relating to tolerability; however, the data were difficult to compare due to variations in the measures used and the outcomes reported.

The use of QoL measures was infrequently and inconsistently reported across all study types, making it difficult to draw conclusions for the older population. There was inadequate data on the use of CGA, which limits the value of the studies to guide treatment decisions.

13.1 Strengths and limitations of the assessment

The main strength of this review is that evidence from a wide range of studies has been included, resulting in a comprehensive evidence base for the treatment of older patients with breast cancer. The review focused on the tolerability of treatment. Data on tolerability, together with efficacy and AE information, can help clinicians to make informed decisions about how to treat older patients with breast cancer.

Using the limited data available, it has been possible to make some comparisons between older and younger patients, which will help to indicate how useful chemotherapy is in clinical practice for this patient population.

However, there are limitations. The populations of the included studies were often very different, even within the disease categories of early breast cancer and advanced or metastatic breast cancer. Studies included patients receiving different lines of treatment and at different disease stages. The inclusion criteria for the selection of studies for the review were deliberately broad, but this has resulted in too much heterogeneity for firm conclusions to be drawn.

There was great variation in the outcome measures utilised in studies and in how these outcomes were reported, and meaningful comparisons of tolerability, QoL and CGA were difficult.

The overall quality of the included studies was poor, and therefore the results must be viewed with caution. Many of the studies selected fitter, healthier patients and the results are not necessarily generalisable to the population of older people seen in routine clinical practice.

Although the results of this review highlight that chemotherapy may be a viable treatment option for older people with breast cancer, 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 meaningful discussions about treatment options.

14 CONCLUSIONS

The results of this review appear to show that chemotherapy can be effective in older patients with breast cancer, and even though there is a higher risk of more serious AEs, chemotherapy can be tolerated.

The efficacy and tolerability data from older patients were broadly similar to data from younger patients, which suggests that age alone should not be a barrier to chemotherapy treatment for breast cancer, and that older age should not disqualify people from being eligible for clinical trials. The results of this review suggest that more studies need to be conducted in older patients with breast cancer to ensure that clinicians and patients together can make informed treatment decisions.

14.1 Suggested research priorities

This review has highlighted the lack of high-quality RCTs designed specifically to investigate the treatment of older people with breast cancer. The RCTs included in this review used many different tools to measure outcomes and often reported them in different ways, making it difficult to compare studies. It is important that future RCTs use consistent analytical methods and outcomes so that comparison and synthesis of results can be conducted in a clinically meaningful way.

Many RCTs focussed solely on one outcome of treatment such as efficacy, or tolerability or QoL. However, the RCT by Muss et al[16] demonstrated that it is possible for one study to collect data on many outcomes, and this is encouraging.

Future trials could include higher proportions of older people, and conducting trials with only older people is certainly feasible and may help to identify the treatments that are both efficacious and well tolerated in this population.

The lack of QoL and CGA data suggests that the development and validation of specific tools of this type are required. The implementation of standardised CGA and QoL measures in future trials may give a clearer picture regarding the eligibility of older people for treatment, and also inform clinicians as to the specific experiences of older people receiving treatment. Given that the evidence shows that (chronological) age in itself should not be the only factor considered when deciding appropriate treatment for patients, it is essential that reliable measures of fitness and comorbidity (characteristics of biological age) are developed and used consistently in both clinical trial settings and routine practice. The development of age-specific QoL measures would yield more useful data; many of the tools used currently in trials have been developed for a general population whose perspective on QoL may be different from that of an older population in terms of relevant outcomes (e.g. maintenance of independence and/or physical appearance).

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16 APPENDICES

Appendix 1: Literature search strategies

Elderly Cancer Search History (35 searches)
Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 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	chemotherap$.tw. or drug therapy.fs.	1734499
19	(adjuvant adj5 chemotherap$).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 (english 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	chemotherap$.tw.	353300
19	(adjuvant adj5 chemotherap$).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 english language and yr="2000 - 2013")**	**4047**

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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
(chemotherap* 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=(chemotherap* 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 will be assessed using criteria based on CRD[9] 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 will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week)*

*** (Concealment will be 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 will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).*

Items will be 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: Table of excluded studies with rationale

Study	Reason for exclusion
Ibrahim 2000[106]	pre 2000
Focan 2001[107]	Comparator
Perez 2001[108]	Protocol only
Colleoni 2002[109]	Population
Crivellari 2002[110]	Comparator
Brancato 2002[111]	Outcomes
Cameron 2003[112]	pre 2000
Maisano 2003[113]	Population
Tominaga 2003[114]	Comparator
D'Hondt 2004[115]	Outcomes
Saek 2004[116]	Outcomes
Fargeot 2004[117]	Comparator
Laloni 2004[118]	Population
Repetto 2004[119]	Outcomes
Doyle 2005[120]	pre 2000
Tan-Chiu 2005[121]	Population
Hurria 2002[122]	Unavailable
Hurria 2005a[123]	Unavailable
Brunello 2006[124]	Unavailable
Elkin 2006[125]	pre 2000
De Matteis 2007[126]	Unavailable
Richardson 2007[127]	Outcomes
Pinder 2007[128]	Outcomes
Clarke 2008[129]	Outcomes
Crawford 2008[130]	Population
Martelli 2008[131]	Comparator
Buist 2009[132]	pre 2000
Mutlu 2009[133]	Population
Brain 2010[134]	Outcomes
Bastiaannet 2010[135]	Outcomes
Klocker 2010[136]	Population
Minckwitz 2010[137]	Protocol only
Ohashi 2010[138]	Population
Brain 2011[139]	Outcomes
Hancke 2011[140]	Comparator
Marinho 2011[141]	Outcomes
Militello 2011[142]	Outcomes
Owusu 2011[143]	Protocol only
Mocerino 2011[144]	Foreign language
Barcenas 2011[145]	Outcomes
Brouckaert 2011[146]	Outcomes
Saxena 2011[147]	Outcomes
Schneider 2011[148]	Outcomes

Mocerino 2012[149]	Foreign language
Barcenas 2012[150]	Outcomes
Chavez-MacGregor 2012[151]	Population
Dialla 2012[152]	Outcomes
Jung 2012[153]	Outcomes
Tarantini 2012[154]	Outcomes
Zucchini 2013[155]	Opinion piece

Appendix 4: Quality of life results

Study	Tool used	Results	Compliance
Early breast cancer			
RCT			
Muss 2009[16]	EORTC QLQ-C30 HADS total (≥15 indicates clinically important anxiety and depression) Linear mixed-effect models used	Standard chemotherapy (CMF or AC): *EORTC QLQ-C30 mean Scores:* Baseline=75.4 (SE1.4) p=0.587 Mid-treatment=63.1 (SE 1.5) p<0.001 End of treatment=63.2 (SE1.4) p<0.001 12 months=78.8 (SE 1.5) p=0.481 18 months=77.4 (SE 1.4) p=0.708 24 months=77.2 (SE 1.5) p=0.775 *HADS mean scores*: Baseline=7.6 (SE 0.4) p=0.947 Mid-treatment=8.8 (SE 0.4) p<0.001 End of treatment=8.2 (SE 0.4) p<0.001 12 months=6.1 (SE 0.4) p=0.746 18 months=5.6 (SE 0.4) p=0.348 24 months=6.0 (SE 6.0) p=0.915 Patients with HADS midtreatment ≥15=18.8% Capecitabine: EORTC QLQ-C30 mean scores: Baseline=76.5 (SE1.5) Mid-treatment=73.1 (SE 1.5) End of treatment=75.8 (SE1.5) 12 months=77.3 (SE 1.6) 18 months=78.2 (SE 1.6) 24 months=76.5 (SE 1.7) HADS. Mean scores: Baseline=7.5 (SE 0.4) Mid-treatment=6.5 (SE 0.4) End of treatment=6.0 (SE 0.4) 12 months=5.9 (SE 0.4) 18 months=6.1 (SE 0.4) 24 months=6.1 (SE 0.5). Patients with HADS midtreatment≥15=6.5%(p=0.002)	Standard chemotherapy (CMF or AC): Patients completing assessment Baseline=170/182 (93%) Mid-treatment=150/182 (82%) End of treatment=153/182 (84%) 12 month=141/182 (78%) 18 month=137/182 (75%) 24 month=137/182 (75%) Capecitabine: Patients completing assessment Baseline=156/168 (93%) Mid-treatment=137/168 (82%) End of treatment=136/168 (81%) 12 month=127/168 (76%) 18 month=114/168 (68%) 24 month=109/168 (65%)
Crivellari 2013[10]	Self-reported QoL with LASA indicators (range 0-100) Physician-administered cognitive functioning (Mini-Cog test; range 0-5) Physician-administered physical functioning (VES; range 0-10)	Patients on PLD reported worse QoL scores than those on non-PLD for all measures (except nausea/vomiting) at most post-baseline time points Overall: Patients with cognitive impairment: Baseline=13/73 (18%) 12 months=5/61 (8%). Assessed at baseline and 12 months: Baseline cognitive impairment=10/59 (17%) 12 months cognitive impairment=5 (8%) Cut-off for being physically vulnerable: Baseline=11/73 (15%) 12 months=16/62 (26%)	PLD: Selected QoL scores*: Physical well-being: 0 months=38 3 months=34 6 months=33 12 months=29 Functional performance: 0 months=38 3 months=35 6 months=34 12 months=30 Overall disease/treatment burden: 0 months=37

Study	Tool used	Results	Compliance
			3 months=35 6 months=34 12 months=29 Mucosa Inflammation: 0 months=38 3 months=35 6 months=33 12 months=30 VES-13 score Physical functioning: 0 months=35 3 months=33 6 months=32 12 months=28 Mini-Cog test Cognitive functioning: 0 months=36 3 months=32 6 months=32 12 months=28 Non-PLD Selected QoL scores: Physical well-being: 0 months=38 3 months=36 6 months=37 12 months=34 Functional performance: 0 months=38 3 months=36 6 months=37 12 months=34 Overall disease/treatment burden: 0 months=37 3 months=36 6 months=37 12 months=34 Mucosa Inflammation: 0 months=38 3 months=36 6 months=37 12 months=34 VES-13 score Physical functioning: 0 months=38 3 months=36 6 months=37 12 months=34 Mini-Cog test Cognitive functioning: 0 months=37 3 months=35 6 months=35

Study	Tool used	Results	Compliance
			12 months=33
Single cohort			
Hurria 2006[73]	FACT-B	Pre, post and 6 month after chemotherapy, Median (range): Physical well-being=26 (9-28), 24 (15-28), 26 (14-28) p=0.59 Social well-being=26 (14-28), 25 (5-28), 25 (0-28) p=47 Emotional well-being=20 (9-24), 22 (12-24), 22 (11-24) p=0.13 Functional well-being=22 (5-28), 23 (3- 28), 23 (9-28) p=0.75 Breast cancer scale=27 (12- 37), 28 (10- 35), 29 (15- 36) p=0.24 Total=117 (80-141), 116 (80- 140), 121 (81- 142) p=0.49	
Ladoire 2011[76]	IADL	44% of patients were dependent in one or more IADL or one significant comorbidity	NA
Claire Dees 2000[61]	BCQ	BCQ cycle 1; mean±SD <65(n=33)=7.74±1.16 ≥65(n=11)=7.65±0.88 p=0.83 BCQ cycle 4; mean±SD <65(n=28)=6.74±1.67 ≥65(n=7)=6.63±1.48 p=0.86 Change in BCQ: <65(n=28)=0.93±1.08 ≥65(n=7)=0.83±1.42 p=0.83	
Watters 2003[84]	QLQ-C30	Physical function (prior to chemotherapy, 3rd cycle, completion and 6 months post): <65=87±17, 80±22, 72±23, 84±21 ≥65=86±16, 88±17, 84±16, 85±21 Old vs young p<0.05 Role function (prior to chemotherapy, 3rd cycle, completion and 6 months post): <65=81±22, 71±27, 66±24, 88±19 ≥65=89±17, 38±20, 68±25, 84±20 Emotional function (prior to chemotherapy, 3rd cycle, completion and 6 months post): <65=68±19, 76±18, 74±19, 78±24 ≥65=81±15, 93±11, 88±11, 82±21 Old vs young p=<0.02 Global health status (prior to chemotherapy, 3rd cycle, completion and 6 months post): <65=69±20, 65±19, 65±17, 75±19 ≥65=78±16, 77±14, 66±20, 73±22	
Browall 2008[59]	EORTC QLQ-C30	Global health, baseline and 4 month follow-up (mean, SD): Younger=75 (18), 70 (22) Older=76 (20), 70 (24) Physical function: Younger=92 (8), 82 (14) Older=87 (17), 79 (19)	

Study	Tool used	Results	Compliance
Advanced or metastatic breast cancer			
RCT			
Feher 2005[12]	23 QoL scales	Statistically significant mean changes between arms: Physical functioning for cycles 1 and 2 (worse for epirubicin) Nausea/vomiting for cycle 1 (worse for gemcitabine) Pain for cycle 5 (worse for gemcitabine) Body image for cycles 1 and 2 (worse for gemcitabine) Arm symptoms for cycles 4 and 5 (worse for gemcitabine) Systemic therapy side-effects for cycles 1, 2, 3, 4 and 5 (worse for gemcitabine)	Epirubicin: Number of questionnaires analysed by cycle: 1=117, 2=110, 3=88, 4=72, 5=61, 6=41 Gemcitabine: Number of questionnaires analysed by cycle 1=113, 2=93, 3=67, 4=43, 5=35, 6=18.
Comparative cohort			
Hess 2007[53]	11 linear analog self-assessment indicators	No substantial changes were observed across time points vs baseline	Completion rates baseline during treatment WOB 87.5 and 91.5% WB 85 and 89%
Single cohort			
Dinota 2005[64]	EORTC QLQ-C30	Month 2: Better=30%, Stable=62%, Worse=8% Month 4: Better=52%, Stable=40%, Worse=37% Month 6: Better=46%, Stable=37%, Worse=17%	
Addeo 2008[55]	EORTC QLQ-C30 IADL ADL	Throughout the six courses of treatment, the score of the EORTC QLQ-C30 showed no significant changes IADL: Index increased=4/27 patients (15%) Index remained stable=20/27 (74%) Index decreased=3/27 (11%) ADL: Improved=2/27 (7%) No change=24/56 (89%) Worsened=1/27 (4%) After six chemotherapy cycles, IADL and ADL indexes improved or remained unchanged in 89 and 96% of evaluable cases, respectively. No significant correlation was observed between ADL and IADL indexes after chemotherapy and the response to the treatment. Moreover, both IADL and ADL changes were not statistically significant (P=0.05)	
Retrospective data			
De Sanctis 2012[89]	Clinical-benefit response as measure of increase in QoL	Patients achieving positive CBR: 42/75 (56%)	NA

EORTC QLQ-C30=EORTC quality of life cancer questionnaire; HADS=Hospital Anxiety and Depression Scale; CMF=cyclophosphamide, methotrexate and 5-fluorouracil; AC=doxorubicin plus cyclophosphamide; SE=standard error; QoL=quality of life; LASA= Linear Analogue Self-Assessment; PLD=pegylated liposomal doxorubicin; VES=Vulnerable Elders Survey; FACT-B=Functional Assessment of Cancer Therapy-Breast; IADL=Instrumental Activities of Daily Living; BCQ=Breast Cancer Chemotherapy Questionnaire; ADL=Activities of Daily Living; CBR=clinical benefit rate

Appendix 5: Comprehensive geriatric assessment results

Study	Results
Early breast cancer	
RCT	
Romieu 2007[21]	VES-13 PP group score: 0=26 (84%) 1=5 (16%)
	SP group score: 0=18 (62%) 1=8 (28%) Other=3 (10%)
Nuzzo 2008[17]	ADL and IADL CMF: ADL at baseline: No activity impaired (score 6)=46/53 (86.8%) At least one activity impaired (score <6)=6/53 (11.3%) IADL at baseline: No activity impaired (score 8)=24/53 (45.3%) At least one activity impaired (score <8)=28/53 (52.8%) ADL missing information=1/53 (1.9%) IADL missing information=1/53 (1.9%)
	Docetaxel: ADL at baseline: No activity impaired (score 6)=40/48 (83.3%) At least one activity impaired (score <6)=8/48 (16.7%) IADL at baseline: No activity impaired (score 8)=27/48 (56.3%) At least one activity impaired (score <8)=21/48 (43.8%) ADL missing information=0 IADL missing information=0
Prospective single cohort	
Hurria 2006[73]	ADL, IADL, GDS, CCI, BMI Pre, post and 6 month after chemotherapy, Median (range): ADL=17 (17-18), 17 (17-18), 17 (17-18) p=0.64 IADL=21 (17-21), 21 (12-21), 21 (19-21) p=0.42 GDS=2 (0-8), 2 (0-9), 1 (0-7) p=0.56 CCI=3 (2-6), 3 (2-7), 3 (2-7) p=0.95 BMI=28 (21-50), 28 (20-47), 28 (19-47) p=0.95 One patient did not complete the tests.
Hurria 2006[73]	ADL, IADL, KPS, CCI, MMS examination, GDS No significant differences in functional status, comorbidity, or depression scores before and 6 months after chemotherapy: ADL p=0.18, IADL p=0.61, KPS p=0.16, CCI p=0.65, GDS p=0.78. All patients completed the tests
Advanced or metastatic breast cancer	
Pooled analyses	
Biganzoli 2007[32]	CIRS-G <70 (PLD every 4/6 weeks) Number of comorbidities (0–2 vs≥3), comorbidity burden scored
	≥70 years (PLD every 4/6 weeks)

	Number of comorbidities (0–2 vs≥3), median number of comorbidities (0–2: 34/50, ≥3: 8/12
Prospective single cohort	
Basso 2007[57]	MGA, CIRS-G MGA scores (not reported) fit=8, vulnerable=3, frail=1. CIRS-G=Only 2 patients had Grade 3-4 comorbidities
Del Mastro 2005[63]	Baseline ADL and IADL data were available for 38 and 36 patients, respectively; at least one ADL dependency was reported in 10 (26.3%) patients and IADL dependency in at least one item was reported in 25 (73.2%) patients Unplanned subgroup analyses were performed to generate hypotheses regarding the possibility that geriatric assessment can help to predict toxicity and activity of treatment. The CCI and IADL scales were never predictive of either toxicity or activity. On the contrary, the presence of at least one inability among those itemised in the ADL scale was significantly associated with both a lower probability of response (p=0.009, Fisher's exact test) and a shorter progression-free survival (p=0.04, log-rank test), but not with unacceptable toxicity rates
Falandry 2011[66]	≥1 ADL deficit: 10%, ≥1 IADL deficit: 82%, nursing home care: 12%; nutritional: albumin ≤35G/L: 26.7%, BMI <21: 20%; psychological: depression 17%; biological: lymphocytes ≤1 g/L: 23% Thus, 23% and 58% reached Fried criteria for frailty and prefrailty
Girre 2008[69]	Baseline, cycle 6 (median score, range) IADL: 8 (4.5-8), 8 (4-8) ADL: 6 (5.5-6), 6 (5.5-6) GDS: 2 (0-11), 3 (1-4)
Retrospective data	
Freyer 2011[91]	ADL/IADL MMS GDS Balducci at diagnosis Mean ADL=3.93 (SD 2.89) Mean IADL=4.57 (SD 3.34) Mean MMS=27.1 ± 2.8 (23-30) Mean GDS=0.75 ± 0.8 (0-2.0) Balducci at diagnosis: Fit=60 (55%) Intermediate=44 (40%) Fragile=6 (5%) Assessment in one or more areas=97 (88%) 2 or 3 evaluations=(46%) MMS=14 (13%) GDS=15 (14%)
Zauderer 2009[101]	CCI 0=118 (73%) 1=29 (18%) 2=11 (7%) 3=4 (2%)

VES=Vulnerable Elders Survey; PP=5-fluorouracil, epirubicin and cyclophosphamide; SP=5-fluorouracil, epirubicin and cyclophosphamide with pegfilgrastim ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; CMF=cyclophosphamide, methotrexate and 5-fluorouracil; GDS=Geriatric Depression Scale; BMI=body mass index; CCI=Charlson Comorbidity Index; KPS=Karnofsky performance status; MGA=Multidimensional Geriatric Assessment; CIRS-G=Cumulative Illness rating Scale for Geriatrics; MMS=Mini-mental Status.