FINAL REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Systematic review to examine the clinical effectiveness and tolerability of systemic anti-cancer therapy for older people with chronic myeloid leukaemia

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Title: Systematic review to examine the clinical effectiveness and tolerability of systemic anti-cancer therapy for older people with chronic myeloid leukaemia

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Abbreviations:

AE	Adverse event
CCI	Charlson Comorbidity Index
CCyR	Complete cytogenetic response
CGA	Comprehensive geriatric assessment
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
DFS	Disease free survival
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
FFS	Failure-free survival
HR	Hazard ratio
IFN-α	Interferon alpha
KPS	Karnofsky performance status
MCyR	Major cytogenetic response
MHR	Major haematological response
MMR	Major molecular response
NCEI	The National Cancer Equality Initiative
NE	Not evaluable
NR	Not reported
OS	Overall survival
PFS	Progression-free survival
Ph+	Philadelphia chromosome positive
POI	Pharmaceutical Oncology Initiative
PS	Performance status
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
TKI	Tyrosine kinase inhibitors

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

1.2 Aims and objectives

The aim of this review is to systematically consider the evidence for the clinical effectiveness and tolerability of systemic anti-cancer therapies used to treat chronic myeloid leukaemia (CML) 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 from electronic searching were assessed for inclusion through two stages. In stage 1, two reviewers independently screened titles and abstracts to identify 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 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 for each study are presented in structured tables and as a narrative summary.

1.4 Results

Electronic searching resulted in 86 references. Manual de-duplication of references resulted in 84 unique references for screening at stage 1. Initial screening identified 33 references, which were obtained as full-text papers. A total of 15 papers met the inclusion criteria at stage 2, and were included in the review.

The 15 studies comprised two subgroup analyses of RCTs, four pooled analyses, three single cohorts, and six retrospective studies.

1.5 Conclusions

The review has highlighted a lack of RCTs designed specifically to address toxicity and efficacy of systemic anti-cancer therapy in older patients. The available data suggest that systemic anti-cancer therapy can be used safely, with good response to treatment and without consistent excess toxicity in older patients.

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 systemic anti-cancer therapy in older patients. However, not all older people are frail; many have good life expectancy and are in good health overall, suggesting that characteristics other than age should be taken into account when assessing the suitability of older people for treatment.

The National Cancer Equity Initiative (NCEI) is focussed on reducing cancer inequalities, which includes improving outcomes for older patients with cancer. In collaboration with the Pharmaceutical Oncology Initiative (POI), the NCEI is seeking to deepen the understanding of current practice in relation to cancer treatment for older people, with the aim of enabling a more personalised treatment protocol, which 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 systemic anti-cancer therapy for this patient population.

2.1 Description of health problem

Chronic myeloid (myelogenous) leukaemia (CML) is a malignant abnormality of haematological stem cells, whereby the production of the granulocyte lineage is greatly enhanced. Though originating from the bone marrow disease, the expanded myeloid mass is seen in the blood and also commonly involves the spleen and occasionally liver and lymph nodes.[1] CML mainly affects adults from middle age, with the median age at diagnosis being 60.[2,3] Fewer than 700 people in the UK are diagnosed with CML each year, representing about 14% of all leukaemias.[4,5]

2.1.1 Aetiology

Gender and age are two common risk factors for CML; more men than women are affected and risk increases with age.[5] However, there are no known hereditary, familial, geographic, ethnic or economic risk factors. In all patients, the leukaemic cells express the characteristic BCR-ABL1 fusion oncogene, and in more than 90% of CML patients a balanced reciprocal translocation between chromosomes 9 and 22 is also seen; this is known as the Philadelphia chromosome.[4,6]

2.1.2 Pathology and prognosis

There are three main phases of CML. The chronic phase is the most stable phase and about 90% of people are diagnosed at this stage. Symptoms during the accelerated phase are more obvious and often include pain associated with an enlarged spleen, fatigue and weight loss. During the blast (acute)

phase, the disease has transformed into acute leukaemia.[7] Symptoms during this phase are more pronounced and response to treatment is only temporary.

Data collected by the National Cancer Intelligence Network (NCIN) suggest that the 5-year survival rate for patients diagnosed with CML is 60%, and for those diagnosed at the chronic stage the figure is 90%.[8] Prognosis is based on the phase of the disease combined with a prognostic index score. The main index is called the Sokal score, which is calculated based on age, spleen size, platelet count and the percentage of blasts (immature white blood cells) in the blood. There are also two newer but similar scoring systems, known as the Hasford (or EUROscore) and the EUTOS (European Treatment and Outcome Study) scores, which use similar parameters to the Sokal score but also include the peripheral blood eosinophil and/or basophil counts at diagnosis.[6] The score indicates the likelihood of achieving complete cytogenetic response (CCyR), with low-risk patients having a higher chance of achieving CCyR than high-risk patients. Older patients, patients with an enlarged spleen, or those in blast phase of CML usually have a poorer prognosis than younger patients.

2.1.3 Current treatment options

The current standard first-line treatments for CML are tyrosine kinase inhibitors (TKIs).[4] Imatinib is the most widely used TKI, followed by nilotinib after imatinib failure. Another recommended second-line therapy is dasatinib, though this is not currently approved by the National Institute for Health and Care Excellence (NICE).[3] Conventional cytotoxic chemotherapy is no longer the standard treatment option for patients with CML, and is rarely used to treat patients in the chronic phase, except in the very rare situation where all TKIs fail. Standard chemotherapy drugs such as hydroxycarbamide (hydroxyurea) or, busulfan, are no longer used routinely for the treatment of CML.[9,10]

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 systemic anti-cancer therapies used to treat CML 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 CML. There is no agreed definition of 'older': the World Health Organisation[11] 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[12] 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 systemic anti-cancer therapy have been considered to ensure that the review is as inclusive as possible.

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 CML
Interventions	Any systemic anti-cancer therapy (all lines of treatment)
Comparators	• an alternative systemic anti-cancer therapy or • best supportive care
Outcomes	Efficacy outcomes: • overall survival • progression-free survival • response rates Tolerability outcomes: • adverse events • tolerability Other outcomes: • Quality of life • Comprehensive geriatric assessment
Other considerations	Papers that reported subgroup analyses for older people in their abstract were included Only studies published since 2000 in full and 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 systemic anti-cancer therapy, 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 of treatment. Therefore, data were extracted from any measure that could be used to determine how much treatment a patient received.

Treatment discontinuations and withdrawals are other measures of how well a patient has tolerated treatment. 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 assess patient eligibility for trials or as an outcome measure to establish how well the patient has responded to treatment in terms of how fit and well they are.

4.3 Data extraction and quality assessment strategy

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

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

4.4 Evidence synthesis

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

5 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

5.1 Number of studies identified

Electronic searching of databases resulted in 86 references. Manual de-duplication of references resulted in 84 unique references for screening at stage 1 (Figure 1).

Initial screening identified 33 references, which were obtained as full-text papers (stage 1). A total of 15 papers met the inclusion criteria at stage 2 and were included in the review. A list of references that were excluded at stage 2 is presented in Appendix 2. The 15 studies included in the review were divided into four categories, based on study design. Table 2 presents the numbers of studies in each category and a brief description of the study type. No RCTs that included only older patients were identified in the search.

Table 2: Categorisation of included studies

Study type	Definition	Number of studies
Subgroup analyses of RCTs	Analyses of RCTs from the general population with elderly/older subgroups reported separately	2
Pooled analyses	Published studies that use aggregated subgroup data on elderly/older patients from RCTs or cohort studies	4
Single cohorts	Studies that report single cohorts of elderly/older patients	3
Retrospective data	Any reports of systemic anti-cancer therapy for elderly/older patients in a defined cohort of patients or as report from registries of patient outcomes	6
Total		**15**

RCT=randomised controlled trial

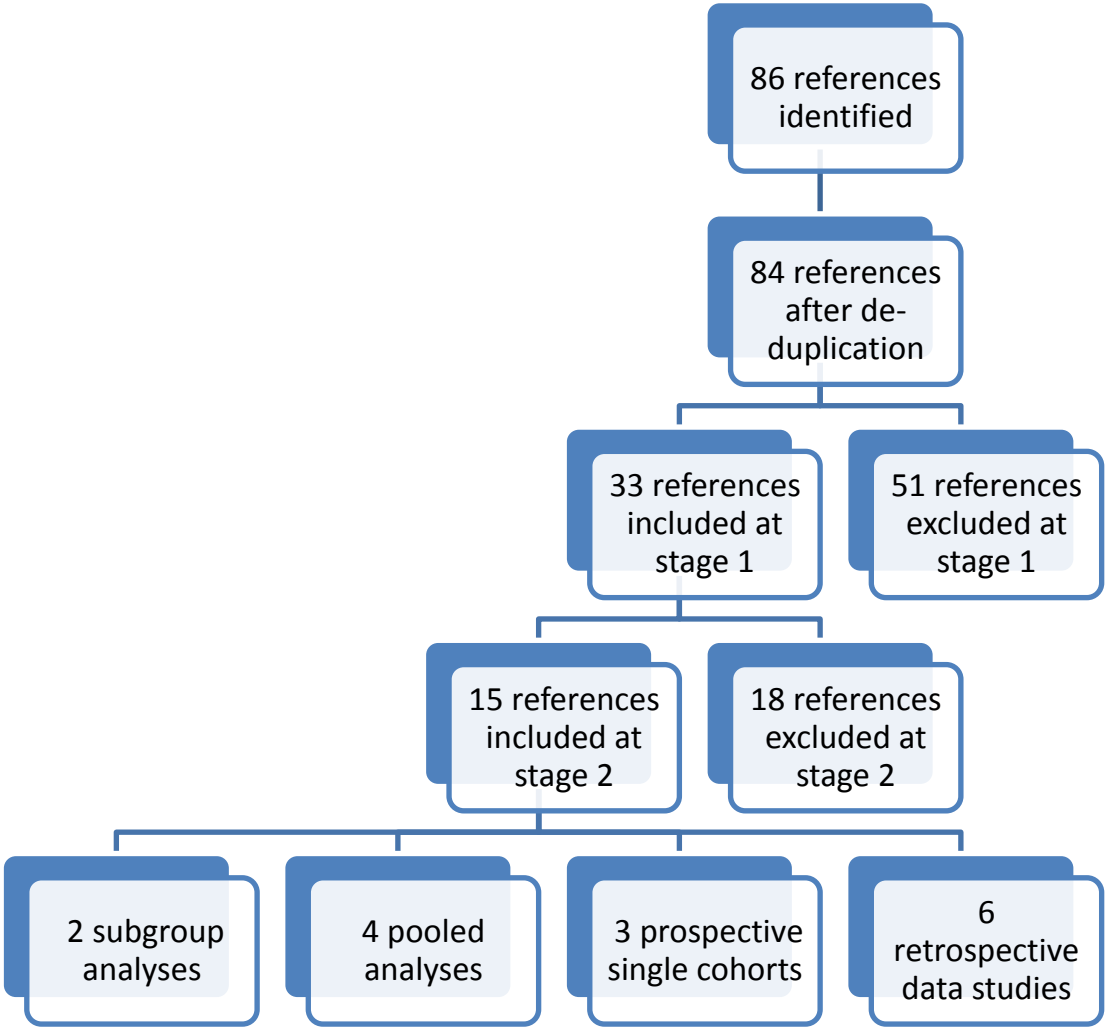

Figure 1: Flow diagram of included studies

6 SUBGROUP ANALYSES OF RANDOMISED CONTROLLED TRIALS

Two studies[13,14] met the inclusion criteria for the reporting of subgroup analyses of older patients in RCTs. Trial and study characteristics are presented in Table 3. Where possible, data regarding age and performance status (PS) are presented; however, both studies were published in abstract form only and some data were not reported by the authors.

6.1 Study characteristics

Both studies were subgroup analyses of multicentre, international RCTs. The data published by Larson et al[14] were from a phase III trial, whereas Gambacorti-Passerini et al[13] did not specify the phase of the RCT. Larson et al[14] did not specify funding information, whereas Gambacorti-Passerini et al[13] was funded by a pharmaceutical company. Neither publication reported the recruitment period of the trial. The studies were similar in size, and both studies included similar proportions of older patients. The definition of older was ≥65 years in both studies.

Both studies recruited patients who were newly diagnosed in the chronic phase. Gambacorti-Passerini et al[13] compared bosutinib with imatinib, and Larson et al[14] compared two doses of nilotinib (300 mg vs 400 mg). Patient baseline data were poorly reported, and neither study specified median age of patients. Larson et al[14] reported that 80% of patients had an Eastern Cooperative Oncology Group (ECOG) PS of 0, but PS data were not presented by Gambacorti-Passerini et al.[13] In both studies, the proportion of older patients with an intermediate to high Sokal risk score was over 90%.

Both studies concluded that treatment was generally well tolerated by older patients who achieved similar response rates to younger patients.

Table 3: Study characteristics, subgroup analyses of randomised controlled trials

Study	Study details	Population	Intervention (n)	Baseline data	Purpose	Author conclusions
Gambacorti-Passerini 2012[13] (abstract only)	Multicentre International Median follow-up 24 months Funded by Pfizer Inc	Chronic phase Newly diagnosed CML ≥65=11.4%	Bosutinib 500 mg/day ≥65=30 <65=220 Imatinib 400 mg/day ≥65=27 <65=225	≥65 Sokal risk: L=4% I=72% H=25% <65 Sokal risk: L=39% I=44% H=17%	To summarise the activity and tolerability of bosutinib 500 mg/day and imatinib 400 mg/day among older vs younger patients	Although the frequency of certain toxicities as well as treatment discontinuations due to TEAEs was higher among older patients, the toxicity profile of bosutinib remained manageable and distinct from that of imatinib regardless of age
Larson 2011[14] (abstract only)	Phase III Multicentre International Median follow-up 24 months	Chronic phase Newly diagnosed CML ≥65=10%	Nilotinib 300 mg ≥65=36 <65=282 Nilotinib 400 mg ≥65=28 <65=281	ECOG PS: 0=80% Sokal risk score: I-H=94%	To evaluate the efficacy and safety of nilotinib 300 mg twice daily and nilotinib 400 mg twice daily in older patients with newly diagnosed CML in chronic phase	Older patients treated with nilotinib demonstrated high rates of cytogenetic and molecular responses and low rates of progression. Nilotinib was generally well tolerated by older patients. In older patients, nilotinib 300 mg had numerically higher rates of CCyR and MMR and was generally better tolerated (as evidenced by fewer AEs and discontinuations) vs nilotinib 400 mg. These data support the use of nilotinib 300 mg in older patients with newly diagnosed CML-chronic phase

CML=chronic myeloid leukaemia; L=low; I=intermediate; H=high; ECOG PS=Eastern Cooperative Oncology Group performance status; CCyR=complete cytogenetic response; MMR=major molecular response; AE=adverse event; TEAE=treatment-emergent adverse events

6.2 Efficacy evidence

6.2.1 Clinical outcomes

Data for clinical outcomes relating to cytogenetic response and haematological response for subgroup analyses are presented in Table 4.

Gambacorti-Passerini et al[13] reported that for patients who received bosutinib, lower rates of CCyR at 24 months were reported for older patients compared with younger patients, and median time to CCyR was shorter (70% by 24 weeks vs 80% by 12.7 weeks). For patients who received imatinib, CCyR rates and time to response were similar in both age groups (78% by 24.4 weeks vs 80% by 24.7 weeks). Similarly, Larson et al[14] reported lower CCyR in older compared with younger patients in both the 300 mg (83% vs 87%) and 400 mg (68% vs 87%) nilotinib arms, although no statistically significant difference was reported.

Larson et al[14] reported similar results for major molecular response (MMR) both across treatment arms and for older versus younger patients: 72% versus 71% for nilotinib 300 mg, and 61% versus 67% for nilotinib 400 mg. Gambacorti-Passerini et al[13] reported a lower rate of MMR in older patients compared with younger patients receiving bosutinib (53% vs 60%), although the median time to MMR was similar (48.1 vs 48 weeks). For patients receiving imatinib, MMR was similar for both older and younger patients (48% vs 49%); however, time to response was longer in the younger age group (84.1 vs 60 weeks).

6.2.2 Efficacy outcomes

Efficacy outcomes for subgroup analyses are presented in Table 5.

Only Gambacorti-Passerini et al[13] presented efficacy outcomes. Bosutinib demonstrated better 2-year event-free survival (EFS) and overall survival (OS) in the older population compared with younger patients (EFS: 100% vs 91%, OS: 100% vs 97%). For patients receiving imatinib therapy, EFS was longer in the younger population (88% vs 81%) as was 2-year OS (95% vs 92%).

Table 4: Clinical outcomes, subgroup analyses of randomised controlled trials

Study	Intervention	MCyR	CCyR	CHR	MMR
Gambacorti-Passerini 2012[13] (abstract only)	Bosutinib 500 mg ≥65	NR	24-month CCyR 70% Median time to CCyR 24 weeks	NR	24-month MMR 53% Median time to MMR 48.1 weeks
	Bosutinib 500 mg <65	NR	80% 12.7 weeks	NR	60% 48 weeks
	Imatinib 400 mg≥65	NR	78% 24.4 weeks	NR	48% 60.6 weeks
	Imatinib 400 mg <65	NR	80% 24.7 weeks	NR	49% 84.1 weeks
Larson 2011[14] (abstract only)	Nilotinib 300 mg ≥65	NR	24-month CCyR 83%	NR	24-month MMR 72%
	Nilotinib 300 mg <65	NR	87%	NR	71%
	Nilotinib 400 mg ≥65	NR	68%	NR	61%
	Nilotinib 400 mg <65	NR	87%	NR	67%

MCyR=major cytogenetic response; CCyR=complete cytogenetic response; CHR=complete haematological response; MMR=major molecular response; NR=not reported

Table 5: Efficacy outcomes, subgroup analyses of randomised controlled trials

Study	Intervention	Median EFS (95% CI)	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)
Gambacorti-Passerini 2012[13] (abstract only)	Bosutinib 500 mg	≥65=2-year EFS 100%	NR	2-year OS 100%	NR
		<65=2-year EFS 91%	NR	2-year OS 97%	NR
	Imatinib 400 mg	≥65=2-year EFS 81%	NR	2-year OS 92%	NR
		<65=2-year EFS 88%	NR	2-year OS 95%	NR

EFS=event-free survival; CI=confidence interval; OS=overall survival; NR=not reported

6.3 Tolerability evidence

Both subgroup analyses[13,14] reported at least one outcome of interest relating to tolerability. Details are presented in Table 6.

Neither study[13,14] reported information relating to dose intensity; however, both studies[13,14] reported data regarding discontinuations and/or withdrawals. Larson et al[14] reported a higher number of withdrawals due to toxicity in older patients compared with younger patients when given nilotinib at a dose of 400 mg (36% vs 10%). However, when given at a dose of 300 mg, the withdrawal rates for older and younger patients were similar (6% vs 9%). Gambacorti-Passerini et al[13] reported a higher number of withdrawals due to AEs with bosutinib (500 mg) in the older patients compared with younger patients (39% vs 22%), and this difference was statistically significant (p=0.023). There was no statistically significant difference in withdrawal rates due to AEs for imatinib when comparing older and younger patients, and these rates were relatively low (8% vs 9%). Gambacorti-Passerini et al[13] reported higher rates of dose interruptions due to AEs in the older population for both treatment regimens (bosutinib: 89% vs 63%; imatinib: 69% vs 42%). Rates of dose reductions for any reason were higher for older patients in the imatinib arm (42% vs 18%) and the bosutinib arm (64% vs 40%).

The most frequently observed grade 3-4 AE reported by Larson et al[14] was elevated glucose, which was more frequently observed in older patients compared with younger patients at the lower 300 mg dose of nilotinib (23% vs 4%). Grade 3-4 neutropenia was observed more frequently in younger patients at both 300 mg (14%) and 400 mg (12%); no cases of grade 3-4 neutropenia were observed in the older population. This was also the case for thrombocytopenia: 12% of younger patients experienced thrombocytopenia with the 300 mg dose of nilotinib compared with no older patients, and 13% of younger patients compared with 4% of older patients experienced thrombocytopenia in the 400 mg dose group. Gambacorti-Passerini et al[13] reported that grade 3-4 neutropenia for bosutinib was 11% for both age groups. Neutropenia was also the most common grade 3-4 toxicity in the imatinib groups, and was only marginally higher in the older population (23% vs 22%).

Table 6: 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
Gambacorti-Passerini 2012[13] (abstract only)	NR	Bosutinib 500 mg ≥65 Discontinuations=57% Discontinuations due to AEs=39%	Dose reductions=64% Interruptions due to AEs=89%	Overall grade 3-4 toxicities=89% Grade 3-4 neutropenia=11%
	NR	Bosutinib 500 mg <65 Discontinuations=35% Discontinuations due to AEs=22% (comparing ≥65, p=0.023)	Dose reductions=40% Interruptions due to AEs=63%	Overall grade 3-4 toxicities=65% Grade 3-4 neutropenia=11%
	NR	Imatinib 400 mg ≥65 Discontinuations=35% Discontinuations due to AEs=8%	Dose reductions=42% Interruptions due to AEs=69%	Overall grade 3-4 toxicities=73% Grade 3-4 neutropenia=23%
	NR	Imatinib 400 mg <65 Discontinuations=28% Discontinuations due to AEs=9% (comparing ≥65, p=0.496)	Dose reductions=18% Interruptions due to AEs=42%	Overall grade 3-4 toxicities=56% Grade 3-4 neutropenia=22%
Larson 2011[14] (abstract only)	NR	Nilotinib 300 mg ≥65 Withdrawn=25% Withdrawn due to toxicity=6%	NR	Neutropenia=0% Thrombocytopenia=0% Elevated glucose=23% Elevated lipase=11%
	NR	Nilotinib 300 mg <65 Withdrawn=25% Withdrawn due to toxicity=9%	NR	Neutropenia=14% Thrombocytopenia=12% Elevated glucose=4% Elevated lipase=7%
	NR	Nilotinib 400 mg ≥65 Withdrawn=46% Withdrawn due to toxicity=36%	NR	Neutropenia=0% Thrombocytopenia=4% Elevated glucose=16% Elevated total bilirubin=12% Elevated lipase=16%
	NR	Nilotinib 400 mg <65 Withdrawn=19% Withdrawn due to toxicity=10%	NR	Neutropenia=12% Thrombocytopenia=13% Elevated glucose=4% Elevated total bilirubin=8% Elevated lipase=7%

AE=adverse event; NR=not reported

6.4 Comprehensive geriatric assessment and quality of life

No studies reported outcomes of comprehensive geriatric assessment or quality of life.

6.5 Summary and discussion

There were two subgroup analyses[13,14] of multicentre, international RCTs included in the review, with only a small percentage of older patients forming the study populations. The therapies investigated were all TKIs (bosutinib, imatinib, and nilotinib). Where reported, baseline data suggest that the patients were representative of older patients seen in practice in the UK. The cut-off age for 'older' patients was ≥65 years.

Both studies[13,14] presented data for CCyR and MMR, and although there was a trend for younger patients to achieve more favourable outcomes than older patients, the results suggest that older patients also derive benefit from TKI therapy treatment. Only Gambacorti-Passerini et al[13] presented outcomes relating to survival.

Data relating to tolerability suggest that treatment is tolerable for older patients, although withdrawal rates were higher for those aged ≥65.

The authors' conclusions suggest that TKI therapy is well tolerated by older patients, and that responses to treatment are similar for older and younger patients.

7 POOLED ANALYSES

Four pooled analyses[15-18] met the inclusion criteria and were included in the review. Study characteristics are presented in Table 7.

7.1 Study characteristics

All studies[15-18] were multicentre and one study[16] was international. Three of the studies[15,16,18] were funded by a pharmaceutical company and one study was supported by research grants.[17] The smallest study was Kantarjian et al,[16] which recruited 223 patients, and the largest study was Berger et al,[18] which recruited 856 patients. The proportion of older patients within each study ranged from 21%[17] to 34%.[16]

Two studies reported the recruitment period, which ran from 1983 to 1994[18] and from 2003 to2007,[17] respectively. All studies focussed on patients in the chronic phase of the disease who had tested positive for the Philadelphia chromosome mutation (Ph+). Two studies[15,16] focussed on second-line treatment, and the other two[17,18] focussed on first-line treatment. The cut-off age for 'older' patients was either ≥60[16,18] or ≥65 years.[15,17] Gulgiotta et al[17] and Kantarjian et al[16] reported patient ECOG PS, which was predominantly 0-1. Berger et al[18] used the Karnofsky performance status (KPS), and again, most patients were in relatively good health (KPS <80% ranged from 8% to 14%).

The authors' conclusions indicate that, in general, response to TKI therapy in older patients is similar to that in younger patients.

Table 7: Study characteristics, pooled analyses

Study	Study details	Population details	Intervention (n)	Baseline data	Purpose	Author conclusions
Brummendorf 2012[15] (abstract only)	Multicentre Median follow-up 31 months Funded by Novartis; Pfizer; ARIAD; Bristol-Myers Squibb & Deciphera Stratification NR	Chronic phase Ph+ Second-line ≥65=33%	Bosutinib 500 mg/day ≥65 (n=88) <65 (n=315)	NR	To measure efficacy and safety of Bosutinib in elderly vs younger CML patients	Bosutinib demonstrated similar efficacy and acceptable safety in both older and younger patients across Ph+ leukaemia cohorts
Gugliotta 2011[17]	Multicentre Italy 2003-2007 Median follow-up 60 months (1-83) Funded by GIMEMA CML Working Party; COFIN 2003; FIRB 2001; Associazione Italiana per la Ricerca sul Cancro; CNR; Fondazione del Monte di Bologna e Ravenna; European Leukemia Net; Bologna AIL Stratification NR	Early chronic phase Ph+ and BCR-ABL+ First-line ≥65=21%	Imatinib ≥65 (n=115) <65 (n=444)	Median age: ≥65=71 years (65-84) All patients=52 (18-84) Male: 60% ≥65 ECOG PS: 1=76% 2=24% <65 ECOG PS: 1=80% 2=20% ≥65 Sokal risk: L=9% I=72% H=19% <65 Sokal risk: L=47% I=30% H=23%	To analyse the difference between age and outcome for early chronic phase CML	Response to imatinib was not affected by age and the mortality rate linked to CML is similar in both age groups
Berger 2003[18]	Multicentre Germany 1983-1994 Median follow-up 7	Chronic phase Ph+ and/or BCR-ABL+ First-line treatment ≥60=23%	≥60 (n=199) IFN α (n=91) Hydroxyurea (n=63) Busulfan (n=45)	Median age: 66 years(60-85) Male: 45.2%	To assess the long-term outcome of older patients with Ph+ and/or BCR-ABL+ CML	We conclude that the course of CML is not different in the elderly. They require lower IFN doses, achieve the same

Study	Study details	Population details	Intervention (n)	Baseline data	Purpose	Author conclusions
	years Funded by German Ministry of Education and Research (BMBF); Competence network 'Acute and chronic leukaemias–01 GI9980/6; Hoffmann-La Roche; Forschungsfonds der fakultat fur Klinische Medizin Stratification NR		<60 (n=657)	KPS: ≥60 <80%=14% <60 <80%=8% New CML score ≥60: L=8% I=61% H=31% <60: L=44% I=42% H=14%		haematological and cytogenetic response rates and the same survival advantage at comparable toxicity
Kantarjian 2002[16]	Multicentre International Median follow-up 17 months (1-21) Funded by Novartis Stratification NR	Chronic phase Ph+ Second-line ≥60=34%	Imatinib 400mg ≥60 (n=67) <60 (n=156)	Male: 57% PS: 0-1=98% 2=2%	To evaluate the incidence and durability of cytogenetic responses over a longer follow-up period and to analyse pre-treatment and therapy-related factors associated with response and survival	Imatinib mesylate is highly effective in chronic-phase CML after IFN-α failure. We identified pre-treatment and treatment-associated factors that were associated with higher major cytogenetic response rates and with improved survival

CML=chronic myeloid leukaemia; Ph+=Philadelphia chromosome positive; IFN-α=interferon alpha; L=low; I=intermediate; H=high; NR=not reported

7.2 Efficacy evidence

7.2.1 Clinical outcomes

Data for clinical outcomes relating to cytogenetic response and haematological response are presented in Table 8.

Only one study[15] presented data for major cytogenetic response (MCyR), with similar rates for older and younger patients treated with second-line bosutinib. Three studies[15,17,18] reported results of CCyR. Berger et al[18] reported no significant difference in CCyR between older and younger patients (10% vs 8%), Gugliotta et al[17] also reported no significant differences in CCyR between the older and younger patients (74% vs 78% at 18 months), and Brummendorf et al[15] reported similar results for older and younger patients, with slightly higher rates for older patients treated with bosutinib after imatinib than for bosutinib after dasatinib/nilotinib (38% vs 23%).

Complete haematological response (CHR) was reported by two studies,[15,17] and results within studies were similar across age groups. MMR was reported by two studies.[16,17] Gugliotta et al[17] reported that there was little difference in MMR rates between older and younger patients treated with imatinib, and Kantarjian et al[16] reported similar figures in each age group (57% vs 65%).

7.2.2 Efficacy outcomes

Efficacy data were available for at least one outcome of interest for all four studies,[15-18] and are presented in Table 9.

One study[17] presented data for rates of progression-free survival (PFS), failure-free survival (FFS) and EFS at 6 years, and reported statistically significantly higher rates for younger patients compared with older patients.

In terms of OS, Berger et al[18] reported a higher OS across all treatment groups for younger patients compared with the older patients. The three remaining studies[15-17] presented data for survival at different time points (2-year, 6-year and 1.5-year), and results were generally comparable between older and younger patients, with the exception of Gugliotta et al[17] who reported statistically significant differences in 6-year OS results: 78% for older patients compared with 92% for younger patients ($p<0.0001$).

Table 8: Clinical outcomes, pooled analyses

Study	Intervention	MCyR	CCyR	CHR	MMR
Brummendorf 2012[15] (abstract only)	Bosutinib cohort 1[a] ≥65	43%	38%	81%	NR
	Bosutinib cohort 1[a] <65	57%	45%	87%	NR
	Bosutinib cohort 2[b] ≥65	27%	23%	72%	NR
	Bosutinib cohort 2[b] <65	34%	24%	74%	NR
Gugliotta 2011[17]	Imatinib ≥65	NR	69% (6 month) 78% (12 month) 74% (18 month)	97% (3 month)	47% (6 month) 58% (12 month) 57% (18 month)
	Imatinib <65	NR	67% (6 month) 77% (12 month) 78% (18 month) vs ≥65, p=0.82, 0.9, 0.38	96% (3 month) vs ≥65, p=0.999	48% (6 month) 59% (12 month) 63% (18 month) vs ≥65, p=0.83, 0.92, 0.24
Berger 2003[18]	IFN-α ≥60 (62% evaluable)	NR	Complete=10% Partial=4% Minor=3% Minimal=12% None=32%	NR	NR
	IFN-α <60 (72% evaluable)	NR	Complete=8% Partial=9% Minor=7% Minimal=16% None=33%	NR	NR
Kantarjian 2002[16]	Imatinib ≥60	NR	NR	NR	57%
	Imatinib <60	NR	NR	NR	65% vs ≥60, p=0.27

IFN-α=interferon alpha; MCyR=major cytogenetic response; CCyR=complete cytogenetic response; CHR=complete haematological response; MMR=major molecular response; NR=not reported
[a] Chronic phase of chronic myeloid leukaemia (CML) after imatinib
[b] Chronic phase CML after dasatinib and/or nilotinib

Table 9: Efficacy outcomes, pooled analyses

Study	Intervention	Median PFS/EFS (95% CI) Months	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value
Brummendorf 2012[15] (abstract only)	Bosutinib after imatinib ≥65 <65	NR NR	NR	2-year survival=87% 2-year survival=92%	NR
	Bosutinib after dasatinib and/or nilotinib ≥65 <65	NR NR	NR	2-year survival=80% 2-year survival=85%	NR
Gugliotta 2011[17]	Imatinib ≥65	6-year EFS 55% (45 to 64) 6-year FFS 62% (52 to 70) 6-year PFS 75% (65 to 83)	EFS p=0.006 FFS p=0.0009 PFS p=0.0001	6-year OS 78% (68 to 85)	p<0.0001
	Imatinib <65	6-year EFS 67% (61 to 72) 6-year FFS 78% (73 to 82) 6-year PFS 90% (86 to 92)		6-year OS 92% (89 to 95)	
Berger 2003[18]	IFN-α	NR	NR	≥60=56 <60=65	NR
	Hydroxyurea	NR	NR	≥60=46 <60=57	NR
	Busulfan	NR	NR	≥60=44 <60=47	NR
Kantarjian 2002[16]	Imatinib ≥60 <60	NR NR	NR	1.5-year survival=96% 1.5-year survival=96%	p=0.98

IFN-α=interferon alpha; PFS=progression-free survival; EFS=event-free survival; FFS=failure-free survival; OS=overall survival; CI=confidence interval; NR=not reported

7.3 Tolerability evidence

One study[18] reported data relating to tolerability outcomes. Details are presented in Table 10.

Berger et al[18] presented information regarding duration of treatment and median daily dose for patients treated with interferon alpha (IFN-α). The median daily dose delivered to patients was statistically significantly higher for younger patients (p=0.011). Rates of withdrawals due to AEs were similar for both older and younger patients (20% vs 18%).

Table 10: 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
Berger 2003[18]	IFN-α (2.5-3.4 x10^6IU/m^2) ≥60 Median duration of treatment=18 months Median daily dose 2.5 Mio IU/m^2/day	Withdrawn due to AEs=20%	NR	NR
	IFN-α (2.5-3.4 x10^6IU/m^2) <60 Median duration of treatment=17 months Median daily dose 3.4 Mio IU/m^2/day (vs ≥60, p=0.011)	Withdrawn due to AEs=18%	NR	NR

IFN-α=interferon alpha; AE=adverse event; NR=not reported

7.4 Comprehensive geriatric assessment and quality of life

No studies reported outcomes of comprehensive geriatric assessment or quality of life.

7.5 Summary and discussion

Four studies[15-18] that presented pooled analyses of data from RCTs were included in the review. The proportion of older patients varied from 21%[17] to 34%.[16] Results from these studies should be interpreted with caution as it is unclear whether the primary RCTs stratified patients by age at randomisation. The studies investigated the use of imatinib,[16,17] bosutinib[15] and the now-obsolete IFN-α/hydroxyurea/busulfan,[18] so this study is of historical interest only. All studies recruited patients with chronic phase disease. Where reported, patient baseline data showed that study populations had a good PS and predominantly low Sokal risk scores.

In terms of clinical outcomes, there were no significant differences between older and younger patients, suggesting that these therapies are viable treatment options for older patients. One study[17] presented statistically significant efficacy results in favour of younger patients compared with older patients for PFS, FFS and EFS at 6 years. Results for survival rates were generally comparable between older and younger patients; however, one study[17] reported statistically significant 6-year OS results in favour of younger patients.

Tolerability data were limited and no conclusions could be drawn from the data available.

The authors' conclusions suggest that response to treatment in older patients is similar to that of younger patients.

8 SINGLE COHORTS

Three single-cohort studies[19-21] met the inclusion criteria and were included in the review. Study characteristics are presented in Table 11.

8.1 Study characteristics

Two of the studies[19,21] were multicentre and one study[20] did not report this information. Two studies[19,20] were conducted in Italy and one study[21] was conducted in Spain. Rosti et al[20] was a phase II study; the phase was not reported in the other two studies.[19,21] Two studies[19,21] received funding from pharmaceutical companies and one study[20] was supported by research grants. Two studies[19,21] recruited only older patients, and one study[20] recruited both older and younger patients, with 20% of the study population aged ≥65 years. The smallest cohort of older patients was Sanchez-Guijo et al,[21] which recruited 36 patients, and the largest study was Breccia et al,[19] which recruited 181 older patients, all of whom were aged >75 years.

All three studies[19-21] investigated the use of imatinib, and were concerned with the chronic phase of the disease, with one study[20] looking more specifically at late chronic phase and including only patients who carried the Ph+ mutation. The definition of 'older' was ≥65 for two studies[20,21] and >75 for one study.[19] Across the studies, the proportion of males was similar. None of the studies reported patient PS; however, Sokal risk scores were presented by Breccia et al,[19] with the majority of patients being at intermediate risk.

Table 11: Study characteristics, single cohorts

Study	Study details	Population	Intervention (n)	Baseline data	Purpose	Author conclusions
Breccia 2011[19] (abstract only)	Multicentre Italy Funded by Novartis	Chronic phase >75=100%	Imatinib (n=181)	Median age: 78.6 years (75-93.6) Male: 52.5% Sokal risk: I=58.0% H=30.4% NE=11%	To observe the impact of concomitant diseases on both compliance and outcome	Our results suggest that treatment of very elderly CML patients might be influenced by personal physician perception: evaluation at baseline of comorbidities according to CCI should improve initial decision making in this subset of patients
Sanchez-Guijo 2011[21]	Multicentre Spain Median follow-up 24 months (2-35) Funded by Novartis	Chronic phase ≥65=100%	Imatinib (n=36)	Median age: 76.6 years (65-87) Male: 47%	To assess the toxicity and outcome of elderly CML patients treated with imatinib	Imatinib displays, in advanced-age patients with chronic phase CML, an efficacy and safety profile comparable to younger patients
Rosti 2007[20]	Phase II Italy Median follow-up 36 months (12-54) Funded by COFIN 2003 (Molecular therapy of Ph-positive leukemias) FIRB 2001; University of Bologna; Italian Association for Cancer Research (A.I.R.C.); Fondazione del Monte di Bologna e Ravenna, European; LeukemiaNet; AIL grants	Late chronic phase Ph+ Interferon resistant/intolerant ≥65=20%	Imatinib 400 mg ≥65 (n=58) <65 (n=226)	Median age: 74 years (65-85) Male: 48%	To assess the effect of age on response and compliance to treatment in patients with CML	Older patients experienced more adverse events, both haematological and non-haematological: this worsened compliance did not, however, prevent a long-term outcome similar to that of younger patients

I=intermediate; H=high; NE=not evaluable; CML=chronic myeloid leukaemia; CCI=Charlson Comorbidity Index

8.2 Efficacy evidence

8.2.1 Clinical outcomes

Data for clinical outcomes relating to cytogenetic response and haematological response are presented in Table 12.

Only one study[20] reported data for MCyR and found that younger patients had higher rates (74%) compared with older patients (53%); the result was statistically significant (p=0.003). All studies[20-22] presented data for CCyR. Rosti et al[20] reported a statistically significantly lower CCyR in older patients compared with younger patients treated with imatinib (36% vs 58%; p=0.002). Sanchez-Guijo et al[21] reported a CCyR of 61% at 6 months, which increased to 83% at 18 months. Breccia et al[19] reported higher CCyR for those with a low Charlson Comorbidity Index (CCI) compared with high CCI (66% vs 57%).

Two studies[20,21] reported data for CHR. Sanchez-Guijo et al[21] reported a CHR of 86% at 6 months, which increased to 94% at 18 months for older patients, and Rosti et al[20] found that the response was statistically significantly lower in older patients compared with younger patients (53% vs 74%; p=0.003). Sanchez-Guijo et al[21] was the only study to report MMR, which was 55% at 12 months and 69% at 18 months.

8.2.2 Efficacy outcomes

Efficacy data were available for at least one outcome of interest for all three studies.[19-21] However, data were limited, as all studies focussed primarily on cytogenetic or haematological response.

One study[19] presented data for EFS, which was higher in patients with low CCI compared with those with a higher CCI score (34 vs 23.5 months). The OS was reported by two studies.[19,21] Breccia et al[19] compared patients with low and higher CCI score, and those with a lower score achieved a higher median OS (40.8 vs 10.6 months). Sanchez-Guijo et al[21] reported only the median OS, which was 34 months.

Table 12: Clinical outcomes, single cohorts

Study	Intervention	MCyR	CCyR	CHR	MMR
Breccia 2011[19] (abstract only)	Imatinib	NR	CCI 0=66% CCI >3=56.5%	NR	NR
Sanchez-Guijo 2011[21]	Imatinib	NR	61% (6 month) 72% (12 month) 83% (18 month)	86% (6 month) 89% (12 month) 94% (18 month)	55% (12 month) 69% (18 month)
Rosti 2007[20]	Imatinib ≥65	53%	36%	53%	NR
	Imatinib <65	74% vs ≥65, p=0.003	58% vs ≥65, p=0.002	74% vs ≥65, p=0.003	NR

MCyR=major cytogenetic response; CCyR=complete cytogenetic response; CHR=complete haematological response; MMR=major molecular response; CCI=Charleston Comorbidity Index; NR=not reported

Table 13: Efficacy outcomes, single cohort

Study	Intervention	Median EFS (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)
Breccia 2011[19] (abstract only)	Imatinib CCI=0	34	NR	40.8	NR
	Imatinib CCI≥3	23.5		10.6	
Sanchez-Guijo 2011[21]	Imatinib	NR	NR	34 (27 to 41)	NR
Rosti 2007[20]	Imatinib	NR	NR	NR	NR

CCI=Charleston Comorbidity Index; EFS=event-free survival; OS=overall survival; CI=confidence interval; NR=not reported

8.3 Tolerability evidence

All three studies[19-21] reported tolerability data. Details are presented in Table 14.

None of the studies[19-21] reported information regarding the dose intensity of treatment administered. Discontinuations were presented by two studies.[19,20] Breccia et al[19] reported higher rates of discontinuation in patients with a lower CCI score (58% vs 48%), and Rosti et al[20] reported slightly higher rates of discontinuation for older patients compared with younger patients (6% vs 2%).

Sanchez-Guijo et al[21] reported only that 19% of patients required a dose reduction from 400 mg to 300 mg due to toxicity. Breccia et al[19] reported a 37.6% rate of reduction for the overall study population.

The most commonly occurring grade 3-4 AE reported by Rosti et al[20] was neutropenia, which was significantly higher in older patients (43% vs 34%; p=0.04). The authors also reported a significantly higher occurrence of thrombocytopenia in older patients (33% vs 20%; p=0.02). Breccia et al[19] reported higher grade 3-4 non-haematological toxicities in patients with a low CCI compared with higher CCI (62% vs 35%). The occurrence of grade 3-4 haematological toxicities was similar for both groups (39% vs 35%).

Table 14: Tolerability evidence, 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
Breccia 2011[19] (abstract only)	NR	Imatinib CCI=0 Discontinuation due to toxicity=58%	Overall dose reduction rate=37.6% (all patients) Reduced standard dose=43.6% Further reduction=39%	Grade 3-4 haematological toxicity=39% Grade 3-4 non-haematological toxicity=62%
	NR	Imatinib CCI≥3 Discontinuation due to toxicity=48%	Reduced standard dose=>50% Further reduction=21%	Grade 3-4 haematological toxicity=35% Grade 3-4 non-haematological toxicity=35%
Sanchez-Guijo 2011[21]	NR	NR	Imatinib 400 mg Interruptions=33.3% Median time of=28 days Dose reduction due to toxicity=19% (400 mg to 300 mg)	NR
Rosti 2007[20]	NR	Imatinib 400 mg ≥65 Discontinued=6%	NR	Neutropenia=43% Thrombocytopenia=33% Non-haematological toxicity=12%
	NR	Imatinib 400 mg <65 Discontinued=2%	NR	Neutropenia=34% (vs ≥65 p=0.04) Thrombocytopenia=20% (vs ≥65, p=0.02)

NR=not reported; CCI=Charlson Comorbidity Index

8.4 Comprehensive geriatric assessment and quality of life

No studies reported outcomes of comprehensive geriatric assessment or quality of life.

8.5 Summary and discussion

Three single cohort studies[19-21] were included in the review. All studies investigated the use of imatinib in patients ≥65/>75 years in the chronic/late chronic phase of the disease. Baseline data were not well reported.

Data for clinical and efficacy outcomes were not comprehensively reported. Results generally suggest that treatment is effective for older patients, with some results favouring the older patients. In terms of tolerability, the rates of discontinuation were similar for older and younger patients; however, rates of haematological toxicity were relatively high for older patients.

The authors' conclusions suggest that efficacy and safety results for the older population are comparable to results for the younger population of patients with CML.

9 RETROSPECTIVE DATA

Six retrospective studies[22-27] met the inclusion criteria and were included in the review. Study characteristics are presented in Table 15.

9.1 Study characteristics

All studies[22-27] were multicentre, four studies[22,23,25,26] were conducted in Italy, one study[24] was conducted in Slovakia and the Czech Republic, and one study[27] was conducted in the UK. One study[27] was funded by a pharmaceutical company; the other studies[22-26] did not provide details of funding. The smallest study was Sheehy et al,[27] which recruited 69 participants, and the largest study was by Faber et al,[24] which recruited a total of 661 participants. Only one study[24] described the recruitment period, which was between 2000 and 2008.

Two studies[22,25] recruited only participants who were in chronic phase disease, two studies[24,27] included >90% of participants in chronic phase and two studies[23,26] did not provide information regarding the phase of disease. The study by Faber et al[24] was predominantly of chronic phase disease (92%), but some patients also had accelerated and blastic phase CML. Three studies[23,24,27] specifically included patients who carried the Ph+ mutation. Four studies were second-line,[22,25-27] one study[24] had a mix of first- and second-line treatments, and the remaining study[23] did not report the line of treatment.

The definition of older was ≥60 years[22,23,25-27] or ≥65 years.[24] None of the studies reported PS, but they did all report Sokal or Hasford scores. Five studies[22-25,27] reported a Sokal risk of low to intermediate for the majority of participants. One study[26] reported only 44% low to intermediate risk, although not all data were available.

Table 15: Study characteristics, retrospective data

Study	Study details	Population	Intervention (n)	Baseline data	Purpose/outcomes	Author conclusions
Tiribelli 2013[23]	Multicentre Italy Median follow-up 21.4 months	Ph+ Imatinib resistant BCR-ABL mutation ≥60=100%	Dasatinib Non-mutated (n=36) Mutated (n=40) N=76	Median age: Non-mutated=70 (60-86) Mutated=70 (60-84) Male: Non-mutated=43% Mutated=53% Sokal risk: Non-mutated L=25% I=40% H=20% NE=15% Mutated L=33% I=39% H=6% NE=22%	To assess the impact of BCR-ABL kinase domain mutations on dasatinib response in elderly CML patients	In elderly patients, detection of BCR-ABL mutations negatively affects response to dasatinib
Breccia 2011[22]	Multicentre Italy	Chronic phase Second-line treatment >60=100%	Dasatinib (n=125)	Median age: 69.9 years (65.4-74.4) Male: 50.4% Sokal risk: L=27% I=39% H=15% NE=20%	To establish associations between comorbidities and the development of pleural effusions or compliance with dasatinib	In elderly patients with chronic CML treated with dasatinib, the rate of drug reduction or suspension and the incidence of pleural effusions seem to be associated with the presence of comorbidities
Faber 2011[24]	Multicentre Czech Republic and Slovakia 2000-2008 Median follow-up 46.1 months (0-122.2)	Chronic phase=92.1% Accelerated phase=5.5% Blastic phase=2.4% Ph+ First-line=57.3% Second-line=29.2% ≥65=10.6%	Imatinib 400 mg ≥65 (n=70) <65 (n=591) N=661	Median age: All patients=51 (15-83) ≥65, first-line=69 (65-81) Second-line=69 (65-80) Male: 54.5% ≥65 Sokal risk: L=10.0% I=56.0% H=33.0%	The observation of treatment preferences and results in patients with CML diagnosed after 2000	The ability to achieve results comparable to those of previous clinical studies in our CML cohort was influenced by centralised care. Decisions not to initiate imatinib or to delay AHSCT may have a negative impact on OS, but comorbidities may limit the treatment potential of

Study	Study details	Population	Intervention (n)	Baseline data	Purpose/outcomes	Author conclusions
				Whole group Sokal risk: L=36.9% I=33.4% H=26.3% ≥65 Hasford risk: L=16% I=66% H=17% Whole group Hasford risk: L=39.3% I=42.7% H=14.7%		imatinib in the elderly
Latagliata 2011[25]	Multicentre Italy Median follow-up 20.7 months	Chronic phase Second-line treatment >60=100%	Dasatinib (n=125)	Median age: At treatment=69.9 (65.4-74.4) At diagnosis=63.1 (58.6-69.2) Male: 50.6% Sokal risk: L=25.5% I=39.2% H=15.2% NE=20%	To describe the tolerability and the efficacy of dasatinib in a wide unselected cohort of older adult patients with CML resistant or intolerant to imatinib	Dasatinib, at the recommended dose of 100 mg/day, is effective and safe also in unselected elderly patients
Porrini 2010[26] (abstract only)	Multicentre National Italy Median follow-up 25 months (0.7-56.3)	Second-line ≥60=100%	Dasatinib ≥60 (n=129) [reduced dose (n=70)]	Sokal risk (for patients in reduced dose cohort): L=16% I=28% H=15%	To evaluate the impact of dose reduction on dasatinib efficacy	Dasatinib given at a lower dose than currently recommended is still effective in elderly CML patients. Very close molecular monitoring is advised when lower doses are prescribed. Studies in larger series are warranted to better define optimal dose and schedule of dasatinib in this frail patient population

Study	Study details	Population	Intervention (n)	Baseline data	Purpose/outcomes	Author conclusions
Sheehy 2008[27]	Multicentre UK Novartis and Bristol-Myers Squibb	Chronic phase=96% Accelerated phase=4% Ph+ Second-line Older ≥60=36%	Imatinib ≥60 (n=25) <60 (n=44) N=69	Median age: 60-69=52% 70-79=28% ≥80=20% Male: 60% Hasford risk: Evaluable=72% L=5.5% I=89.0% H=5.5%	To compare survival and molecular response rates in elderly patients with younger patients presenting with CML since the introduction of imatinib	No significant survival difference was found when this group was compared with younger patients. In the elderly group, 53% of those with molecular data (36% of all elderly patients) had a major molecular response as assessed by real-time quantitative PCR

Ph+=Philadelphia chromosome positive; L=low; I=intermediate; H=high; NE=not evaluable; NR=not reported; CML=chronic myeloid leukaemia; AHSCT=Autologous Hematopoietic Stem Cells Transplantation; OS=overall survival; PCR=polymerase chain reaction

9.2 Efficacy evidence

9.2.1 Clinical outcomes

Data for clinical outcomes relating to cytogenetic response and haematological response are presented in Table 16.

Five studies[23-27] presented outcomes of interest; however, none of the studies reported data for MCyR. Tiribelli et al[23] reported statistically significantly higher rates of CCyR for non-mutated patients than mutated patients treated with dasatinib (57% vs 31%; p=0.05), and Latagliata et al[25] found that older patients had a higher CCyR with 100 mg than 140 mg. Porrini et al[26] reported much lower CCyR for older patients (24.3%). Where comparisons between older and younger patients were reported, Faber et al[24] reported statistically significantly higher rates for patients aged <65 compared with those aged ≥65 for both first- and second-line treatment (p=0.017 and p=0.099, respectively). Sheehy et al[27] reported a higher CCyR for older patients than younger patients (91% vs 52%).

Results for CHR suggest that younger patients fare better than older patients. Faber et al[24] reported that patients aged <65 had a significantly higher CHR than those aged ≥65 for both first- and second-line imatinib (p=0.032 and p=0.115, respectively). Two studies reported CHR for elderly patients receiving dasatinib therapy and these results were comparable.[25,26]

Four studies[23,25-27] reported data on MMR. Tiribelli et al[23] reported better MMR outcomes for non-mutated patients than for mutated patients (37% vs 17%; p=0.11), and Sheehy et al[27] reported that older patients taking imatinib had a higher MMR rate than their younger counterparts (53% vs 36%).

9.2.2 Efficacy outcomes

Four studies[23,24,26,27] reported efficacy outcomes. Details are presented in Table 17.

Three studies[23,24,26] presented data regarding PFS/EFS; however, the results for Tiribelli et al[23] were incomplete. Porrini et al[26] reported an EFS of 21.3 months for older patients treated with dasatinib. Faber et al[24] compared PFS for older and younger patients receiving first- and second-line imatinib but these were not found to be statistically significant (p=0.963 and p=0.406).

Three studies[24,26,27] presented data on OS. Porrini et al[26] reported an OS of 27.3 months for older patients treated with dasatinib. For both first- and second-line treatment, Faber et al[24] reported a significant survival advantage for younger patients (p<0.001). Sheehy et al[27] reported that patients aged 60 or older had a worse survival rate than younger patients (p=0.052) but no data were presented.

Table 16: Clinical outcomes, retrospective studies

Study	Intervention	MCyR	CCyR	CHR	MMR
Tiribelli 2013[23]	Dasatinib ABL non-mutated	NR	57%	NR	37%
	Dasatinib ABL mutated	NR	31% vs mutated, p=0.05	NR	17% vs mutated, p=0.11
Faber 2011[24]	Imatinib first-line ≥65	NR	53.2%	85.1%	NR
	Imatinib first-line <65	NR	71.3% vs ≥65, p=0.017	94.3% vs ≥65, p=0.032	NR
	Imatinib second-line ≥65	NR	47.8%	73.9%	NR
	Imatinib second-line <65	NR	67.5% vs ≥65, p=0.099	87% vs ≥65, p=0.115	NR
Latagliata 2011[25]	Dasatinib 140 mg	NR	42.3%	34.6%	11.5%
	Dasatinib 100 mg	NR	58.1%	23.6%	20%
	Dasatinib all patients	NR	49.1%	27.8%	15.6
Porrini 2010[26] (abstract only)	Dasatinib >60	NR	24.3%	25.7%	15.7%
Sheehy 2008[27]	Imatinib ≥60	NR	91%	NR	53%
	Imatinib <60	NR	52%	NR	36%

MCyR=major cytogenetic response; CCyR=complete cytogenetic response; CHR=complete haematological response; MMR=major molecular response; NR=not reported

Table 17: Efficacy outcomes, retrospective data

Study	Intervention	Median EFS (95% CI) Months	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)
Tiribelli 2013[23]	Dasatinib Non-mutated	Not reached	NR	NR	NR
	Dasatinib Mutated	14.2		NR	
Faber 2011[24]	Imatinib First-line	NR	PFS ≥65 vs <65, p=0.963	NR	OS ≥65 vs <65, p<0.001
	Imatinib Second-line	NR	PFS ≥65 vs <65, p=0.406	NR	OS ≥65 vs <65, p<0.001
Porrini 2010[26] (abstract only)	Dasatinib (>60)	21.3	NR	27.3	NR
Sheehy 2008[27]	Imatinib	NR	NR	NR	p=0.052

EFS=event-free survival; OS=overall survival; PFS=progression-free survival; CI=confidence interval; NR=not recorded

9.3 Tolerability evidence

Five studies[22,23,25-27] reported tolerability data for at least one outcome of interest. Results are presented in Table 18.

Discontinuations were reported by three studies.[25-27] Latagliata et al[25] reported discontinuations due to toxicity for dasatinib 140 mg compared with 100 mg (15.2% vs 53.6%), Porrini et al[26] reported discontinuations due to intolerance (11.4%), and Sheehy et al[27] reported that one patient discontinued imatinib due to oedema.

Dose modifications or treatment interruptions were reported by three studies.[22,23,25] Tiribelli et al[23] reported that 15% and 11% of delays were due to toxicity in non-mutated and mutated groups, respectively. Breccia et al[22] reported a statistically significant difference for both the number of dose reductions (p=0.0001) and the number of dose delays (p=0.0002) between the lowest and highest CCI groups. Latagliata et al[25] reported statistically significantly higher rates of dose reductions due to toxicity in the dasatinib 140 mg group compared with the 100 mg group (88.4% vs 26.7%; p<0.001).

Breccia et al[22] reported that 100% of patients with the highest comorbidity index (3-4) experienced grade 3-4 adverse events, compared with 78% for CCI 0, 43% for CCI 1 and 36% for CCI 2. Latagliata et al[25] reported statistically significantly higher rates of haematological toxicities in the dasatinib 140 mg group compared with the 100 mg group (50% vs 19.6%; p=0.001)

Table 18: Tolerability evidence, 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
Tiribelli 2013[23]	Dasatinib non-mutated Mean±SD dose=94±25 mg	NR	Delays due to toxicity=15%	NR
	Dasatinib mutated Mean±SD dose=101±19 mg	NR	Delays due to toxicity=11%	NR
Breccia 2011[22]	Dasatinib 300-800 mg Median duration of treatment=46.6 months (21.8-61.8)	NR	Increased dose in 46.4% of patients	NR
	NR	NR	CCI=0 Dose reductions=49% Delays=29%	Grade 3-4 haematological toxicity= 78%
			CCI=1 Dose reductions=63% Delays=46%	Grade 3-4 haematological toxicity= 43%
			CCI=2 Dose reductions=74% Delays=58%	Grade 3-4 haematological toxicity= 36%
			CCI=3-4 Dose reductions=100%, p=0.0001 Delays=100%, p=0.0002	Grade 3-4 haematological toxicity= 100%
			ACE27=0 Dose reductions=39% Delays=10%	Grade 3-4 haematological toxicity= 25%
			ACE27=1 Dose reductions=4% Delays=21%	Grade 3-4 haematological toxicity= 14%
			ACE27=2 Dose reductions=68% Delays=40%	Grade 3-4 haematological toxicity= 39%
			ACE27=3 Dose reductions=61% Delays=77% Reduction p=0.02 Delay p=0.0001	Grade 3-4 haematological toxicity= 15%
Latagliata 2011[25]	NR NR	Dasatinib 140 mg Discontinuations due to	Dose reductions due to toxicity=88.4% 100 mg=26.7%	Haematological toxicities=50.0% Non-haematological=30.7%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		toxicity=15.2%	(All patients=53.6%)	
		Dasatinib 100 mg Discontinuations due to toxicity=53.6%	Dose reductions due to toxicity=26.7% (vs 100 mg, p<0.001)	Haematological toxicities=19.6% (vs 140 mg, p=0.001) Non-haematological=21.4%
Porrini 2010[26] (abstract only)	NR	Dasatinib 100 mg Discontinuations due to intolerance=11.4%	NR	NR
Sheehy 2008[27]	NR	Imatinib Discontinuations=4% (1 patient), due to oedema	NR	NR

NR=not reported; CCI=Charlson Comorbidity Index; ACE27=adult comorbidity evaluation 27

9.4 Comprehensive geriatric assessment and quality of life

No studies reported outcomes of comprehensive geriatric assessment or quality of life.

9.5 Summary and discussion

Six retrospective studies[22-27] were included in the review. Reporting of study and patient characteristics was poor; where reported, the studies focussed on patients in the chronic phase. None of the studies reported PS; however, Sokal risk scores for older patients were low. The cut-off age for 'older' patients was ≥60/≥65 years, which was lower than in some of the studies discussed previously.

For clinical outcomes, where comparisons were presented, older patients often achieved more favourable outcomes than younger patients for CCyR and MMR. However, there were statistically significant results favouring younger patients for survival outcomes. Tolerability data were difficult to compare due to the limited data available and the differences in how data were reported.

The authors' conclusions suggest that the presence of BCR-ABL mutations negatively affects response to dasatinib. Other studies concluded that treatment is effective and safe for some older patients, but comorbidities can negatively affect outcomes.

10 DISCUSSION

This review included 15 studies[13-27] that investigated the use of systemic anti-cancer therapy to treat older patients with CML.

No RCTs that enrolled only older patients were identified, and this is perhaps a reflection of the fact that CML is not a common cancer and therefore the organisation of a multinational trial may not be feasible. Four study types were included in the review: subgroup analyses of RCTs, pooled analyses of RCTs, single-cohort studies and retrospective studies. The methodological quality of the included studies is questionable as study characteristics were often poorly reported. In addition, the studies that recruited only older patients were relatively small, as were the proportions of older patients in studies of the general CML population. Studies primarily investigated the use of TKI therapies (imatinib, dasatinib, bosutinib and nilotinib); however, one study[18] investigated the use of IFN-α, hydroxyurea, or busulfan, which are now rarely given to CML patients in any phase but blast crisis.

Where reported, baseline data (e.g. age, PS, Sokal risk score) were generally representative of the characteristics of older patients with CML seen in routine practice in the UK. All studies that reported stage of disease included patients in the chronic phase, with mainly low to intermediate Sokal risk scores, which indicates a good response to treatment. As anticipated, one of the findings of this review is that there is no agreed definition to describe the age (or age range) of 'older' patients recruited to CML studies; the age of patients described as 'older' in the included studies was most commonly ≥60 or ≥65 years.

Reporting of clinical outcomes relating to cytogenetic and haematological responses was good; almost all studies reported data on one or more of these outcomes. Efficacy outcomes such as PFS/EFS, and OS were not reported as comprehensively as other outcomes, and there was variability in how outcome measures were reported, which made it difficult to make comparisons across studies. Although two-thirds of studies reported data relating to tolerability outcomes, the data were difficult to interpret due to the variations in measures used and the nature of the outcomes reported. Taking all of this into consideration, this review presents a limited evidence base to support the view that systemic anti-cancer therapy is effective for older people with CML and that treatment may confer survival benefit to older patients. Studies generally conclude that systemic anti-cancer therapy is a feasible treatment option for older people with CML.

There was no reporting of the use of CGA or QoL measures, which reflects a lack of use in clinical practice. This may be due to practical reasons such as limited resources, or the accepted practice of using PS or Sokal risk scores as an appropriate assessment for study eligibility and/or suitability for treatment.

10.1 Strengths and limitations of the review

The main strength of this review is that evidence has been drawn from a range of study designs in order to build up a comprehensive evidence base to describe systemic anti-cancer treatment in older patients with CML. This review focusses not only on survival and response to treatment, but also on tolerability, which is often a key factor in the decision-making process for both clinicians and patients. Although data were limited, it has been possible to compare results for efficacy and tolerability outcomes between older and younger patients.

The inclusion criteria of this review were deliberately broad in order to include all studies of older patients with any phase of CML. The review did not identify any RCTs that recruited only older patients, and therefore the evidence base is derived from studies that utilised a less-robust methodology and are predominantly small. It is therefore difficult to draw conclusions, and comparisons across study designs and treatment regimens are not necessarily meaningful. Although the results of this review highlight that systemic anti-cancer therapy is a viable treatment option for older people with CML, 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.

11 CONCLUSIONS

The review has highlighted a lack of RCTs designed specifically to assess the tolerability and efficacy of systemic anti-cancer therapy in older patients. The available data suggest that systemic anti-cancer therapy can be safely used, with good response to treatment and no consistent excess toxicity in older patients. Where comparisons were made between older and younger patients, the evidence shows that although younger patients often achieve better responses to treatment than older patients, systemic anti-cancer therapy can be used to treat patients with CML regardless of age, which is certainly reflective of current clinical practice.

11.1 Suggested research priorities

Given that the risk of CML increases with age, and that the median age at diagnosis is 60 years, older patients are underrepresented in clinical studies. The lack of RCTs recruiting only older patients is perhaps a factor that needs to be addressed in order to synthesise good-quality evidence on the efficacy and tolerability of systemic anti-cancer therapy for older patients with CML.

It would be useful to standardise how outcomes relating to tolerability are measured and reported; the tolerability outcomes used in the studies were often reported differently. It is interesting that none of the studies measured QoL, which could give a clearer picture of what happens to older people who undergo systemic anti-cancer therapy, for example in terms of improvements or decline in overall wellbeing, pain, and fatigue. Development of standardised tools that measure toxicity and QoL for future trials would be useful.

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13 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: Table of excluded studies with rationale

Study	Reason for exclusion
Katawani 2001[28]	Population
Portlock 2002[29]	Not CML
Anstrom 2004[30]	Eco model
Rea 2006[31]	Not all CML
Fruehauf 2007[32]	Population
Kanda 2008[33]	Population
Mounier 2012[34]	Not CML
Trask 2012[35]	Population
Efficace 2011[36]	Outcomes
Bjorkholm 2011[37]	Treatment
Bittencourt 2008[38]	Outcomes/population
Brunner 2012[39]	Treatment
Efficace 2010[40]	Outcomes
Ferrero 2011[41]	Outcomes
Gugliotta 2010[42]	Population
Qian 2011[43]	Outcomes
Quintas-Cardama 2011[44]	Treatment/population
Rea 2011[45]	Population