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 renal cell carcinoma

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Title: Systematic review to examine the clinical effectiveness and tolerability of systemic anti-cancer therapy for older people with renal cell carcinoma

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Abbreviations:

AE	Adverse event
CGA	Comprehensive geriatric assessment
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
FKSI	Functional Assessment of Cancer Therapy-Kidney Symptom Index
FACT-G	Functional Assessment of Cancer Therapy-General
HR	Hazard ratio
KPS	Karnofsky performance status
NCEI	National Cancer Equity Initiative
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
POI	Pharmaceutical Oncology Initiative
PFS	Progression-free survival
PS	Performance status
PWB	Physical Well-Being
QoL	Quality of life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
TTP	Time to disease progression

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

1 EXECUTIVE SUMMARY

1.1 Background

Older people with cancer are less likely to receive radical treatment, 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 more personalised treatment protocols, which take into account fitness, choice and benefit to the individual.

1.2 Aims and objectives

The aim of this review is to systematically review the evidence for the clinical effectiveness and tolerability of systemic anti-cancer therapy used to treat renal cell carcinoma (RCC) in older people.

1.3 Methods

Search strategy

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

Study selection

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

Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in an Excel spread sheet using a sample of included studies, and then 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 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.

1.4 Results

Electronic searching of databases resulted in 31 unique references available for screening at stage 1. Initial screening identified 15 references to which inclusion criteria were applied. Nine studies (reported in 11 references) were included at stage 2. The nine studies included in the review were divided into categories, based on study design.

In total, there were data from two retrospective subgroup analyses of RCTs, one pooled analysis, two single cohorts and four retrospective studies.

1.5 Conclusions

The review highlights that selected patient populations can benefit from systemic anti-cancer therapies despite older age; however, it is not possible to draw firm conclusions as to whether less fit older patients would benefit from treatment.

2 BACKGROUND

Older people with cancer are less likely to receive radical treatment.[1] There are a number of reasons for this, including comorbidities and/or frailty associated with older age, and older people are more likely to experience unpleasant side-effects of treatment. However, not all older people are frail; many have good life expectancy and are in good health overall. Older patients represent a heterogeneous patient population with varying degrees of fitness, functional status and co-morbidities, and making decisions simply based on age alone may lead to inequities in the provision of care.

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 more personalised treatment protocols, which take into account fitness, choice and benefit to the individual.

Older patients are underrepresented in clinical trials, and those who do participate 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

Renal cell carcinoma (RCC) is the most common form of kidney cancer, accounting for 80% of all kidney cancers diagnosed.[2] Kidney cancer is the eighth most common cancer in the UK, with over 10,000 people diagnosed in the UK in 2011. Incidence rates have increased by approximately one-third in the past decade, and three-quarters of new cases are diagnosed in people aged over 60.[2]

There are two main histological sub-types of RCC: the majority are 'clear cell' and the remainder are 'non-clear cell' types, which includes papillary, chromophobe, oncocytic, medullary and collecting duct.

2.2 Aetiology

Kidney cancer is not common in people younger than 45 years, and the disease is more common in men than women (3:2 ratio).[3] In the period 2009-11 in the UK, 74% of kidney cancer deaths were in people aged over 65 years. It is estimated that 42% of kidney cancer cases in the UK are attributable to excess weight and smoking.[3]

2.2.1 Pathology and prognosis

In the UK in 2006, approximately 40% of patients with kidney cancer presented with stage III/IV disease, and 50% of those patients who underwent curative surgery for early-stage disease went on to

develop advanced or metastatic disease. The prognosis is poor for patients with advanced or metastatic RCC; the 5-year survival rate is 10% for patients with RCC.[4]

2.3 Current treatment options

Treatment options for RCC are dependent on the age and general health of the patient, in addition to the stage and grade of the cancer.

The only proven curative option is surgical removal of the kidney, which may have a role in palliating symptoms and prolonging survival in selected patients with metastatic or advanced disease.[5] Conventional anti-cancer drug treatments such as cytotoxic chemotherapy are not effective for most types of RCC, and although the tumour can also be resistant to radiotherapy, this treatment modality can have a role in the palliation of symptoms. For decades the mainstay of controlling metastatic disease was through the use of immunotherapeutic drugs such as interferon-α and interleukin-2. These drugs have significant toxicities and overall poor efficacy. For some patients, however, they induced profound and durable radiological responses and may have even been curative in a small minority of patients.

In 2007, the multi-targeted tyrosine kinase inhibitor sunitinib was licensed for the treatment of metastatic RCC after a large randomised trial[6] demonstrated superior efficacy over interferon-α. This marked a new era in the management of metastatic RCC, and since then, a number of targeted treatments have emerged with proven activity against metastatic disease. Although these drugs are very different to conventional cytotoxic chemotherapy, they do have a number of unpleasant and potentially serious side-effects that limit their use. Whether they may have a detrimental effect on the functional status of patients has never been proven, and for some patients these agents may do more harm than good.

3 AIMS AND OBJECTIVES

3.1 Objectives

The aim of this review is to systematically review the evidence for the clinical effectiveness and tolerability of systemic anti-cancer therapies used to treat RCC 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 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 RCC. There is no agreed definition of 'older'; The World Health Organisation[7] 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[8] describes geriatric medicine as being mainly concerned with people aged over 75 years. 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 regards to the stage of disease, tumour histology or the line of treatment described in the literature.

All forms of systemic anti-cancer therapy commonly used for metastatic RCC were considered. In the UK targeted and biological therapies are commonly used in the National Health Service (NHS), either as treatments approved by the National Institute for Health and Care Excellence (NICE) or via the Cancer Drugs Fund.

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 renal cell carcinoma
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 or • progression-free survival • response rates Tolerability outcomes • adverse events • tolerability Other outcomes • use of quality of life measures • use of comprehensive geriatric assessment
Other considerations	Papers that reported subgroup analyses of older people in their abstract were included Only studies published since 2000 in full or with an English language abstract were included

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 some 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 they received. Common

measures reported in studies are the mean or median number of cycles delivered per patient, how many completed the treatment or the relative dose intensity of treatment. Any measure that gave information which could be used to determine how much treatment patients received was extracted from the data.

Treatment discontinuations and withdrawals are other measures of how well a patient has tolerated treatment, and therefore any detailed information such as discontinuation due to toxicity, withdrawal of consent, disease progression or death, for example, were data extracted.

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

Randomised controlled trials (RCTs) commonly report AEs, therefore all reported AEs of grade 3 or higher which were >10% were data extracted, together with any information on toxic deaths.

Geriatric assessment

Comprehensive geriatric assessment is often carried out to determine an older person's health, both physically and mentally, 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 spread sheet 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; disagreements were resolved through discussion with a third reviewer where necessary.

No universally accepted standardised quality assessment tool exists for use with non-randomised studies. There are also a multitude of study designs, and therefore even where appropriate tools exist, applying them is problematic and of limited comparative value. 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 RESULTS

5.1 Quantity and quality of research available

Electronic searching of databases resulted in the identification of 33 potentially relevant references. Manual de-duplication of references resulted in 31 unique references available for screening at stage 1. Details are summarised in Figure 1.

Initial screening identified 15 references, which were obtained as full-text papers. Nine studies (reported in 11 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 2. The nine studies included in the review were divided into categories based on study design. Table 2 presents the number of studies in each category and a brief description of the study type.

Table 2: Categorisation of included studies

Study type	Definition	Number of studies
Retrospective subgroup analyses of randomised controlled trials	Analyses of RCTs from the general population with elderly/older retrospective subgroup analyses reported separately	2
Pooled analysis	Pooled data from published RCTs	1
Single cohort	Studies which report on single cohorts of elderly/older patients	2
Retrospective data	Any reports of systematic anti-cancer treatment for elderly/older patients in a defined cohort of patients or from registries of patient outcomes	4
Total		**9**

RCT=randomised controlled trial

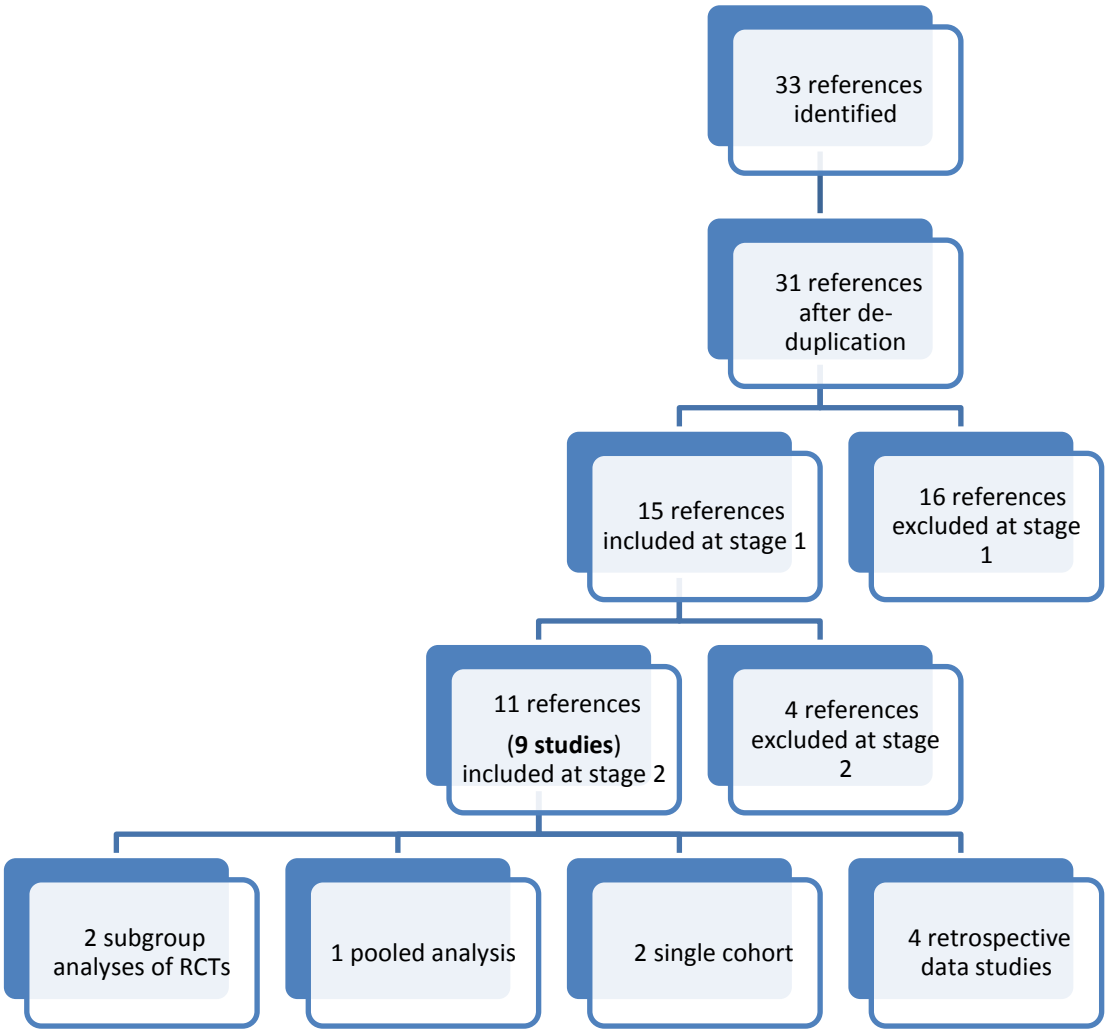

Figure 1: Flow diagram of included studies

5.2 Study characteristics of included studies

Details of study characteristics are presented in Table 3. A total of nine studies (in 11 publications)[9-19] were included in the review, three of which[11,12,15,16] were reported as abstracts only. Two studies[13,17] reported retrospective subgroup analyses from RCTs, one study[15,16] reported pooled data from RCTs, one study[10,18] reported retrospective subgroup analyses from a large single cohort, one study[19] reported outcomes from a large open-access programme, and four studies[9,11,12,14] reported retrospective analyses using data from medical records.

The studies varied in design, and none of the included studies was quality assessed. The size of studies varied; the smallest study was Coward et al[11] with 62 patients and the largest was Gore et al[19] which enrolled 4371 patients. The pooled analysis and single cohort studies were the largest, including >1000 patients, subgroup analyses of RCTs were smaller with <1000 and the smallest studies were the retrospective studies with <200 patients. For those studies that analysed subgroups of older patients, the proportion of older patients varied; the highest proportion of older patients was 59%[14] and the lowest was just 13%.[13] The cut-off age for 'older' (or elderly) was 60 years in one study,[14] 65 years in two studies[17,19] and 70 in the remaining studies.[9-13,15,16,18]

All studies were multicentre with the exception of Coward et al.[11] Four studies[11,12,14-16] did not report the source of funding, and the five that did[9,10,13,17,19] all received support from pharmaceutical companies.

All studies focussed on advanced or metastatic RCC. Where reported, the majority of patients across studies had a performance status (PS) of 0-1, and the proportion of males was above 50%. The lowest median age of the older patients only was 69 years,[17] and the highest was 74 years.[9,12,17]

In terms of treatment, six studies[9,11,12,14-16,19] administered sunitinib, two studies[10,13,18] investigated the use of sorafenib, one study[17] administered everolimus and two studies[13,17] had compared systemic anti-cancer therapy with a placebo.

Table 3 Study characteristics

Study	Study details	Population	Intervention	Baseline data	Purpose	Author conclusions
Subgroup analyses of RCTs						
Porta 2012[17]	Retrospective subgroup analysis of RCT (RECORD I) Multicentre Europe, USA Funded by Novartis Pharmaceuticals Corporation	Metastatic RCC Disease progression on or within 6 months of stopping treatment with sunitinib, sorafenib, or both Aged ≥65=153 (37%) Aged ≥70=73 (18%)	Everolimus plus BSC (n=277) ≥65=112 (40%) ≥70=53 (19%)	≥65 Median age: 69 years (65-85) Male: NR ≥70 Median age: 74 years (70-85) Male: NR	To evaluate the efficacy and safety of everolimus in elderly patients (those aged ≥65 and ≥70 years) enrolled in RECORD I	Everolimus is effective and tolerable in elderly patients with metastatic RCC. When selecting targeted therapies in these patients, the specific toxicity profile of each agent and any patient comorbidities should be considered
			Placebo plus BSC (n=139) ≥65=41 (29%) ≥70=20 (14%)	≥65 Median age: 69 years (65-79) Male: NR ≥70 Median age: 72.5 years (70-79) Male: NR		
Eisen 2008[13]	Retrospective subgroup analysis of RCT (TARGET) Multicentre International France, Poland, Germany, USA 2003-2005 Funded by Bayer Healthcare Pharmaceuticals TARGET was not designed to detect statistically significant differences between older and younger	Advanced RCC Aged <70=787 (87%) Aged ≥70=115 (13%)	Sorafenib (n=451) ≥70=70 (16%)	Median age: 72 years (70-86) Male: 62.9% ECOG PS: 0=29 (41%) 1=39 (56%) 2=2 (3%)	Retrospective subgroup analysis of data from a phase 3 RCT that examined the safety and efficacy of sorafenib in 115 older (age ≥70 years) and 787 younger (age <70 years) patients with advanced RCC	Among patients with advanced RCC receiving sorafenib treatment, outcomes of older (≥ 70 years) and younger (<70 years) were similar
			Placebo (n=452) ≥70=45 (10%)	Median age: 73 years (70-84) Male: 77.8% ECOG PS: 0=25 (56%) 1=20 (44%)		

Study	Study details	Population	Intervention	Baseline data	Purpose	Author conclusions
	patients					
Pooled analyses						
Hutson 2012[15,16] (abstract only)	Retrospective pooled analysis of 6 RCTs Multicentre	Metastatic RCC First-line=74% Second-line=26% Aged <70=857 (81%) Aged ≥70=202 (19%)	Sunitinib (n=1059)	Median age: ≥70=73 <70=57 Male: <70=73% ≥70=59%	To compare PFS and OS between older and younger patients	In patients with metastatic RCC, the efficacy of sunitinib was comparable in the elderly population, deriving similar benefit as younger patients regardless of treatment setting. The AE profiles were also similar, although some AEs were more common in elderly patients
Single cohort						
Bukowski 2010[10,18]	Retrospective subgroup analysis of a single cohort study (ARCCS) Multicentre US and Canada 2005-2006 Funded by Bayer AG and Onyx Pharmaceuticals Inc	Unresectable, recurrent or metastatic RCC Previous systemic therapy=50% Aged <70=1760 (71%) Aged ≥70=736 (29%)	Sorafenib (n=2496)	Male: <70=72% ≥70=63%	In this retrospective analysis of the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) program in North America, the safety and efficacy of sorafenib in patients aged <70 was compared with those aged ≥70 years	There were no substantial differences in safety and efficacy between patients aged <70 and ≥70 years with advanced RCC treated with sorafenib
Gore 2009[19]	Phase II Subgroup analysis of a single cohort study Multicentre International 52 countries: North, Central, and Latin America, Europe, Asia-Pacific, Australia, and Africa 2005-2007 Funded by Pfizer Inc.	Metastatic RCC Previous treatment=73% Aged <65=2953 (68%) Aged ≥65=1418 (32%)	Sunitinib (n=4371)	Median age: 59 years (18-89) Male: 74% ECOG PS: 0=1823 (42%) 1=1872 (43%) 2=503 (12%) 3=73 (2%) 4=6 (<1%)	The primary objective was to provide sunitinib to patients who did not have access to the drug, but who had the potential to derive clinical benefit Secondary objectives included assessment of toxicity and efficacy and to examine these parameters in subgroups with a poor prognosis	In a broad population of patients with metastatic RCC, the safety profile of sunitinib 50 mg once-daily (initial dose) on schedule of 4 weeks on treatment, 2 weeks off was manageable and efficacy results were encouraging, particularly in subgroups associated with poor prognosis who are not usually entered

Study	Study details	Population	Intervention	Baseline data	Purpose	Author conclusions
						into clinical trials
Retrospective studies						
Brunello 2013[9]	Retrospective review of medical charts Multicentre Italy 2006-2010 Funded by Pfizer	Advanced RCC Prior nephrectomy=91.2% Older=≥70	Sunitinib (n=68)	Median age: 74 years (70-88) ECOG PS: 0=19 (27.9%) 1=40 (58.8%) 2=9 (13.3%)	Charts of elderly patients treated with sunitinib for metastatic RCC were reviewed in 6 Italian centres to assess AEs (primary objective), efficacy and correlation of toxicity with CGA (secondary objectives)	Treatment with sunitinib is effective in elderly patients; yet early interruptions were frequent. Starting treatment at reduced dose and escalating in the absence of severe toxicity could be suggested
Coward 2011[11] (abstract only)	Retrospective analysis of patients from single institution United Kingdom 2007-2010	Metastatic RCC >70=24 (38.8%) ≤70=38 (61.2%)	Sunitinib (n=62)	PS 2: ≤70=3 (8%) >70=11 (58%)	To compare tolerability, response rates and median survival of older vs younger patients	Elderly patients more commonly require dose reduction due to poor PS and toxicity profile. The ORR is lower with the lower dose intensity; however, the rate of disease stabilisation is comparable in both groups. The lower dose of sunitinib is well tolerated in the elderly and this regimen should be considered for older patients with poor PS
De Giorgi 2012[12] (abstract only)	Retrospective review of clinical files Multicentre Italy 2006-2011	Metastatic RCC First-line Older=≥70	Sunitinib (standard regimen or adapted regimen) (n=154)	Median age: 74 years (70-88)	To compare standard vs adapted regimen in patients aged ≥70	Sunitinib is active and feasible in patents with metastatic RCC aged ≥70 years. Adapted regimen does not appear to influence PFS and OS and has a favourable impact on toxicity
Elfiky 2011[14]	Retrospective analysis of medical records Multicentre US	Metastatic clear cell RCC Failed sorafenib or bevacizumab	Sunitinib (n=71)	Male: 43 (61%) ECOG PS: 0=21 (30%) 1=26 (37%)	To identify factors that can be used to identify metastatic clear cell RCC patients more likely to benefit from sequential	Metastatic clear cell RCC patients with anaemia have less clinical benefit from sequential sunitinib after failure of

Study	Study details	Population	Intervention	Baseline data	Purpose	Author conclusions
	2004-2008	<60=29 (41%) ≥60=42 (59%)		2=10 (14%)	sunitinib	bevacizumab or sorafenib. Other factors associated with poor outcome include brain metastases, older age, and <1 year between diagnosis and first treatment. Importantly, no difference in outcomes was observed if sequential therapy was initiated within or after 30 days. External validation and prospective evaluation are needed to confirm these findings

RCT=randomised controlled trials;RCC=renal cell carcinoma; BSC=best supportive care; ECOG PS=Eastern Cooperative Oncology Group performance status; PFS=progression-free survival; OS=overall survival; ORR=overall response rate; AE=adverse event

5.3 Efficacy evidence

Outcomes for progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) are presented in Table 4. All studies presented at least one efficacy outcome of interest. Seven studies[10,12-19] presented results for PFS, and one study[9] reported time to disease progression (TTP). Eight studies[9-12,14-19] reported median OS, and six studies[9,11,13,14,17,19] presented ORR.

5.3.1 Sunitinib

Six studies[9,11,12,14-16,19] investigated the use of sunitinib for older patients with RCC, with results derived from pooled analyses, single cohorts or retrospective studies. The patient populations were heterogeneous and the study methods were not robust. None of the studies demonstrated statistically significant results for comparisons between older and younger patients.

Results for median PFS varied greatly, from 5.77 months[14] to 11.3[19] months. One study reported median TTP of 13.6 months[9] for older patients. Where comparisons with younger patients were made, results were similar between older and younger patients. Hutson et al[15,16] found that patients receiving second-line treatment achieved shorter PFS and OS than those receiving first-line treatment; no ORRs were reported for this study. Elfiky et al[14] reported that although older and younger patients achieved similar results for PFS, younger patients had a higher ORR. Coward et al[11] also found that younger patients achieved a higher ORR than older patients, and that results for OS were the same for older and younger patients.

Results for OS were similar across studies and median OS ranged from 15.8[15,16] months to 25.5[15,16] months for older patients. Where comparisons with younger patients were presented it was found that survival times were similar for older and younger patients.

5.3.2 Everolimus

One study[17] investigated the use of everolimus plus best supportive care (BSC) versus placebo plus BSC in older patients with RCC. The results for PFS were statistically significantly improved for patients aged ≥65 and ≥70 receiving everolimus ($p<0.001$). However the results for OS were not significant.

5.3.3 Sorafenib

Two studies investigated the use of sorafenib; Bukowski et al[10,18] reported results from a single cohort treated with sorafenib and the subgroup analyses reported by Eisen et al[13] compared sorafenib with placebo. Bukowski et al[10,18] found that PFS and OS outcomes were similar for older and younger patients. Eisen et al[13] reported PFS but not OS; sorafenib achieved a higher PFS versus placebo in patients aged ≥70, and the ORR was higher for patients aged ≥70 than for those aged <70 (15.7% vs 8.7%).

5.3.4 Summary

On the basis of the available evidence, there appears to be a trend for older patients to achieve similar results to younger patients in terms of PFS, OS and ORR. However, results must be viewed with caution as the populations are heterogeneous, and so the findings are not derived from good quality studies with robust methodology.

Table 4: Efficacy evidence

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
Subgroup analyses of RCTs							
Porta 2012[17]	Everolimus ≥65	5.4	0.33 (0.21 to 0.51) p=< 0.001	14.78 (11.96 to 20.27)	1.07 (0.69 to 1.67) p=0.381	2.7	NR
	Placebo ≥65	2.2		16.13 (8.48 to 22.93)		0	
	Everolimus ≥70	5.1	0.19 (0.09 to 0.37) p=< 0.001	13.57 (9.82 to 21.82)	0.85 (0.47 to 1.55) p=0.301	3.8	NR
	Placebo ≥70	1.9		13.63 (5.09 to 22.93)		0	
Eisen 2008[13]	Sorafenib <70	5.5 (5.2 to 5.9)	Vs placebo <70 0.55 (0.47 to 0.66) Vs placebo >70 0.43 (0.26 to 0.69)	NR	NR	8.7	NR
	Sorafenib >70	6.0 (5.4 to 9.2)		NR	NR	15.7	NR
	Placebo <70	2.7 (2.5 to 2.9)		NR	NR	1.5	NR
	Placebo >70	3.2 (1.6 to 4.2)		NR	NR	4.4	NR
Pooled analyses							
Hutson 2012[15,16] (abstract only)	Sunitinib	<70=9 ≥70=10.9 First-line: <70=9.9 (8.3 to 10.7) ≥70=11 (9 to 14.7) Second-line: <70=8.1 (7.8 to 8.7) ≥70=8.4 (6.3 to 14.2)	0.85 (0.7 to 1.02) p=0.0830	<70=23.3 ≥70=23.7 First-line: <70=23.5 (21.1 to 27.6) ≥70=25.5 (21.6 to 38.4) Second-line: <70=20.1 (16.2 to 25) ≥70=15.8 (13.7 to 23.9)	0.94 (0.76 to 1.15) p=0.5441	NR	NR

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
Single cohorts							
Bukowski 2010[10,18]	Sorafenib <70	9.7 (8.3 to 11)*	p=0.8	11.5 (10.8 to 12.2)	p=0.4	NR	NR
	Sorafenib ≥70	8 (7.6 to 10.6)*		10.6 (9.7 to 12.2)		NR	NR
Gore 2009[19]	Sunitinib All	10.9 (10.3 to 11.2)	NR	18.4 (17.4 to 19.2)	NR	17	NR
	Sunitinib >65	11.3 (10.7 to 12.3)		18.2 (16.6 to 19.8)		17	
Retrospective studies							
Brunello 2013[9]	Sunitinib	TTP: 13.6	NR	18.3 First-line: 17.8 Pre-treated: 18.3	Fit vs unfit** p=0.07	43.3	NR
Coward 2011[11] (abstract only)	Sunitinib	NR	NR	≤70=23 >70=23	NR	≤70=36 >70=21	NR
De Giorgi 2012[12] (abstract only)	Sunitinib	10.6 (8.7 to 15.3)	NR	20.1 (15.5 to not reached)	NR	NR	NR
Elfiky 2011[14]	Sunitinib <60	5.80 (4.60 to 9.03)	p=0.4210	NR (21.27 to NR)	p=0.0496	20.69	p=0.2979
	Sunitinib ≥60	5.77 (3.93 to 9.50)		NR (10.47 to NR)		9.52	

RCT= randomised controlled trial; PFS=progression-free survival; TTP=time to progression; OS=overall survival; ORR=overall response rate; CI=confidence interval; NR=not reported

*Six months after study initiation, sorafenib became commercially available in the USA (December 2005). At that time, the expanded access programme was ended, and patients receiving sorafenib as first-line therapy and/or patients with non-clear-cell renal cell carcinoma enrolled at any US site were eligible to enter a 6-month extension of the protocol designed to assess PFS. All other patients remaining on sorafenib therapy were switched to the commercially available drug

**As determined by comprehensive geriatric assessment

5.4 Tolerability evidence

Results relating to tolerability are presented in Table 5. Three studies[14-16,19] did not report outcomes related to tolerability. Outcomes were not always reported consistently and are difficult to interpret and compare.

5.4.1 Sunitinib

Three studies[9,11,12] presented tolerability results for sunitinib. Brunello et al[9] and De Giorgi et al[12] presented the median cycles per patient, which were quite different: 7.6 versus 4 cycles, respectively. Results for grade 3 fatigue were similar in Brunello et al[9] and Coward et al[11] for older patients (17.6% and 16%), and these figures were slightly higher than those reported for the younger patients (9.6% in Coward et al[11]). Dose reductions were also higher for older patients compared with younger patients in Coward et al.[11] De Giorgi et al[12] compared a standard regimen with an adapted regimen, and found that although discontinuation rates were similar for both regimens, the standard regimen had statistically significantly higher rates of grade 3-4 AEs compared with the adapted regimen (65% vs 42%, p=0.008).

5.4.2 Sorafenib

Bukowski et al[10,18] reported a similar median daily dose for older and younger patients, and all outcomes relating to tolerability were comparable across the two age groups. Eisen et al[13] reported higher rates of permanent discontinuations and dose reductions in older patients.

5.4.3 Everolimus

Porta et al[17] compared everolimus with placebo in patients aged ≥65 and ≥70 and found that treatment duration was longer for patients treated with everolimus. Dose reductions and interruptions due to AEs were much higher for the everolimus arm for both age groups compared with the placebo arm.

5.4.4 Summary

The evidence suggests that sunitinib and sorafenib are less well tolerated in the older population. Despite the limited the evidence, everolimus appears to be tolerable, which reflects the findings of health care professionals in clinical practice.

Table 5: Tolerability evidence

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
Subgroup analyses of RCTs				
Porta 2012[17]	Everolimus ≥65: Median treatment duration=157 (20 to 451) Mean dose intensity, mg/day=9.03 (2.7 to 10.0)	NR	No. of dose reductions/interruptions 0=56(50.5%) 1=30 (27%) >1=25 (22.5%) Due to: AE=44 (39.6%) Dosing error=13 (11.7%) Laboratory test abnormality=6 (5.4%) Scheduling conflict=2 (1.8%)	Anaemia=14% Infection=11% Lymphopenia=9%
	Placebo ≥65: Median treatment duration=84 (21 to 284) Mean dose intensity, mg/day=9.96 (9.3 to 10.0)	NR	No. of dose reductions/interruptions 0=34 (87.2%) 1=5 (12.8%) >1=0 (0%) Due to: AE=3 (7.7%) Dosing error=1 (2.6%) Laboratory test abnormality=1 (2.6%) Scheduling conflict=0 (0%)	Anaemia=3% Infection=3% Lymphopenia=0%
	Everolimus ≥70: Median treatment duration=150 (28 to 402) Mean dose intensity, mg/day=8.69 (2.7 to 10.0)	NR	No. of dose reductions/interruptions 0=23 (44.2%) 1=13 (25%) >1=16 (30.8%) Due to: AE=27 (51.9%) Dosing error=4 (7.7%) Laboratory test abnormality=3 (5.8%) Scheduling conflict=2 (3.8%)	Anaemia=12% Infection=12% Lymphopenia=10%
	Placebo ≥70: Median treatment duration=111 (25-237) Mean dose intensity, mg/day=9.97 (9.4-10.0)	NR	No. of dose reductions/interruptions 0=18 (90%) 1=2 (10%) >1=0 (0%) Due to: AE=2 (10.0%) Dosing error=0 (0%)	Anaemia=0% Infection=0% Lymphopenia=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
			Laboratory test abnormality=0 (0%) Scheduling conflict=0 (0%)	
Eisen 2008[13]	Sorafenib: Tolerated treatment: <70=350 (91.8%) >70=55 (78.6%)	Permanent discontinuations: <70=31 (8.1%) >70=15 (21.4%)	Dose reductions: <70=43 (11.3%) >70=15 (21.4%)	Grade 3 <70=29.4% Grade 3>70=40.0% Grade 4<70=7.3% Grade 4>70=5.7%
Single cohorts				
Bukowski 2010[10,17]	Sorafenib <70: Median daily doses=770 mg	Discontinuations due to AE=8%	Dose reductions=34% Due to AE=30% Dose interruptions=59%	Hand-foot skin reaction=179 (10%)
	Sorafenib ≥70: Median daily doses=733 mg	Discontinuations due to AE=13%	Dose reductions=37% Due to AE=33% Dose interruptions=64%	Hand-foot skin reaction=58 (8%)
Retrospective studies				
Brunello 2013[9]	Sunitinib: Median cycles per patient=7.6 (1 to 26) Mean total dose=7.497 mg	Interrupted therapy in 10 patients (14.7%), due to: Rapidly progressive disease=10.3% Severe toxicity=4.4%	Start-up dose: 50 mg=67.7% 37.5 mg=23.5% 25 mg=8.8% Dose reduction in 69.2%: Upfront=32.4% (due to frailty) After 1st cycle=17.6% Subsequent cycles=19.1% 25 patients starting at full dose required reduction 9 patients starting on 37.5 mg required reduction 1 patient starting at 25 mg required reduction 60.3% dose interruption after median of 4 cycles (due to disease progression/toxicity)	Grade 3 fatigue=17.6%

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
Coward 2011[11]	NR	NR	Sunitinib: Dose reductions after 1st or 2nd cycle=24 (38.7%) ≤70=12 (33%) >70=11 (59%) Started on lower dose (37.5 mg): ≤70=3 (8%) >70=11 (58%)	Grade 3: ≤70 PPE=18% Mucositis=18% Diarrhoea=1.6% Fatigue=9.6% Grade 3:>70 PPE=1.6% Mucositis=8% Diarrhoea=10% Fatigue=16%
De Giorgi 2012[12]	Sunitinib: Median cycles per patient=4	Discontinuations due to therapy-related AEs: Standard regimen (SR)=23% Adapted regimen (AR)=21% (p=0.967)	Standard regimen=68.8% Sunitinib 50 mg/day 4 week on/2 week off Adapted regimen=31.2% 37.5 mg/day, 4week on, 2 week off= 32 patients 25 mg/day, 4 week on, 2 week off= 12 patients 37.5 mg once daily dosing= 4 patients Patients with AR: ≥75=56% <75=32%, P=0.008	Grade 3-4 toxicities: Standard regimen=65% Adapted regimen=42%, p=0.008

RCT=randomised controlled trial; AE=adverse event; NR=not reported; PPE=palmar-plantar erythema

5.5 Geriatric assessment and quality of life

Results for CGA and quality of life (QoL) are presented in Table 6.

One study[9] reported the use of a CGA, and used the Cumulative Illness Rating Scale-Geriatric (CIRS-G) to assess patients at baseline in order to categorise them as either fit, vulnerable, or frail.

Use of a QoL instrument was reported by only one study.[13] The Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI), and the Physical Well-Being (PWB) domain of the Functional Assessment of Cancer Therapy-General (FACT-G) were used to measure QoL. However, there were no significant results when sorafenib was compared with placebo in older patients.

Table 6: Comprehensive geriatric assessment and quality of life

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Summary results**
Eisen 2008[13]	NR	NR	FKSI PWB domain of FACT-G	Among younger patients, the median number of days to health status deterioration as measured by the FKSI-15 tool was 90 days for sorafenib-treated patients and 52 days for placebo-treated patients (HR=0.69, 95% CI=0.59 to 0.81). When measured by PWB, medians were 93 and 73 days (HR=0.69, 95% CI=0.58 to 0.81). Among older patients, sorafenib treatment, compared with placebo treatment, also delayed the time to health status deterioration (121 vs 85 days, HR=0.66, 95% CI=0.43 to 1.03, when measured by the FKSI-15 tool; and 126 vs 84 days, HR=0.65, 95% CI=0.42 to 1.01, when measured by PWB), although neither delay was statistically significant
Brunello 2013[9]	CIRS-G (Cumulative Illness Rating Scale-Geriatric)	Used as baseline measure to stratify patients into fit/vulnerable/frail categories	NR	NR

CIRS-G=Cumulative Illness Rating Scale-Geriatric; FKSI=Functional Assessment of Cancer Therapy – Kidney Symptom Index; PWB=Physical Well-Being; FACT-G=Functional Assessment of Cancer Therapy – General; HR=hazard ratio; CI=confidence interval; NR=not reported

6 DISCUSSION

The World Health Organisation[7] states that most countries in the developed world have accepted the chronological age of 65 years as a definition of 'elderly' or 'older' whereas the British Geriatrics Society[8] describes geriatric medicine as being mainly concerned with people aged over 75. 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 RCC studies; the age of patients described as 'older' in the included studies ranged from >60 to >70 years. This is not necessarily reflective of clinical practice, as clinical expertise suggests a patient over the age of 75 is considered as older. Similarly, most patients in the included studies have a better PS than those seen in routine clinical practice, where patients are more likely to have a PS of >2 and have more co-morbidities. Results should therefore be viewed with caution as they are not necessarily generalisable to the older patient population seen in clinical practice. However, data may be generalisable to the subgroup of older patients seen in routine clinical practice who are generally fit and healthy.

The review has identified a limited number of studies in which older patients are treated for RCC, which is reflective of current clinical practice – older people with RCC are often not eligible for trial entry due to poor PS and general ill health. From the data available describing outcomes related to response and survival, the trend shows that in general, older patients can achieve similar results to their younger counterparts. However, in terms of tolerability, older patients do not appear to tolerate treatment with systemic anti-cancer therapies, perhaps suggesting that patients and clinicians should be cautious when discussing treatment options in order to make the most appropriate decisions for the patient's care to be made, as grades 3-4 toxicity can be fatal in older patients.

There was a lack of data presented for the use of CGA and QoL measures, which mirrors 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 as an appropriate assessment for trial eligibility and suitability for treatment.

6.1 Strengths and limitations

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

Factors contributing to the limitations of this review include the inclusion criteria were deliberately broad to ensure that all older patients with RCC were included, but which resulted in an evidence base derived from predominantly small and methodologically poor studies. It has therefore been difficult to

draw conclusions or conduct meaningful comparisons across patient populations, study designs and treatment regimens. Although the results of this review highlight that systemic anti-cancer therapy may be a viable treatment option for older people with RCC, 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.

7 CONCLUSIONS

The review highlights that selected patient populations with good PS, and adequate renal, hepatic and cardiac functions can benefit from systemic anti-cancer therapies despite older age. It is not possible to draw firm conclusions as to whether less fit older patients would benefit from treatment.

The tolerability evidence does show increased grade 3-4 AE rates for older patients compared with younger patients, which may significantly reduce QoL and could have fatal consequences for older patients, however the data are limited.

The treatments discussed in the review involve repeated trips to hospital for scans and blood tests and are associated with toxic side effects and only a few months of added life expectancy, on average. Given that metastatic RCC can pursue an indolent course, with older patients dying with RCC rather than from RCC, it is of the utmost importance that discussions take place between older patients and clinicians to allow patients to opt for the most appropriate treatment pathway.

7.1 Considerations for future research

The lack of QoL and CGA data in the review suggests that the development and implementation of standardised CGA and age-specific QoL measures in future clinical trials is needed. Use of such tools may give a clearer picture regarding the eligibility of older people for treatment and also inform clinicians about the specific experiences of older people receiving treatment.

Given the toxicity profiles of sunitinib and sorafenib, it would be advisable to investigate the use of lower doses or modified schedules in older patients with RCC. In addition future trials designed to investigate the use of everolimus in the treatment of older patients with RCC would be informative, because of the lower AE rates associated with this treatment.

8 REFERENCES

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9 APPENDICES

Appendix 1: Literature search strategies

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

# ▲	Searches	Results
1	exp Breast Neoplasms/	206832
2	(breast$ adj5 (neoplasm$or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	57204
3	exp Colorectal Neoplasms/	139935
4	(colorectal adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	63395
5	exp Lung Neoplasms/	165165
6	(lung adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	116112
7	exp Carcinoma, Renal Cell/	20951
8	((renal cell or kidney) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	21641
9	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ or exp Leukemia, Myeloid, Chronic-Phase/ or exp Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative/	15723
10	(chronic myel$ adj2 leuk?emia).ti,ab.	19580
11	exp Lymphoma, Non-Hodgkin/	80985
12	(Lymphoma$ adj5 (non-hodgkin$ or non hodgkin$)).ti,ab.	28219
13	or/1-12	663599
14	*"Aged, 80 and over"/ or *Aged/	21737
15	(senil$ or geriatr$ or older or elder$ or late-life or later-life or late$ life).ti,ab.	392827
16	14 or 15	401572
17	13 and 16	15012
18	33hemotherapy$.tw. or drug therapy.fs.	1734499
19	(adjuvant adj5 chemotherap$).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 (33hemoth 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	34hemotherapy$.tw.	353300
19	(adjuvant adj5 chemotherap$).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 34hemoth language and yr=”2000 – 2013”)**	**4047**

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

[Breast Neoplasms] explode all trees 7763
breast cancer* or breast neoplasm* or breast tumour* or breast carcinoma*:ti,ab,kw (Word variations have been searched) 14703
[Colorectal Neoplasms] explode all trees 4628
“colorectal cancer”:ti,ab,kw (Word variations have been searched) 4311
[Lung Neoplasms] explode all trees 4272
“lung cancer”:ti,ab,kw (Word variations have been searched) 6836
[Carcinoma, Renal Cell] explode all trees 419
kidney cancer or renal cell cancer:ti,ab,kw (Word variations have been searched) 789
[Leukemia, Myelogenous, Chronic, BCR-ABL Positive] explode all trees 304
“chronic myeloid leukaemia”:ti,ab,kw (Word variations have been searched) 101
[Lymphoma, Non-Hodgkin] explode all trees 1136
non-hodgkin’s lymphoma:ti,ab,kw (Word variations have been searched) 1203
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 30561
(senil* or geriatr* or older or elder* or late-life or later-life or late*):ti,ab,kw (Word variations have been searched) 67255
Aged] explode all trees 554
#14 or #15 67394
#13 and #16 2332
(35hemotherapy* 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=(35hemotherapy* 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: Excluded studies

Study	Reason for exclusion
Ramos-Barcelo 2009[20]	Study design
Gernone 2011[21]	Outcomes
Keilholz 2011[22]	Outcomes
Procopio 2013[23]	Pools studies included in review