EUROPEAN JOURNAL OF CANCER 47 (2011) 1458–1467

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Review

Critical review of economic evaluations in multiple myeloma: An overview of the economic evidence and quality of the methodology

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ARTICLE INFO

Article history:
Received 25 November 2010
Received in revised form 29 March 2011
Accepted 4 April 2011
Available online 9 May 2011

Keywords:
Multiple myeloma
Economics
Methodology
Decision-making
Pharmacoeconomics
Review

ABSTRACT

Continued expansion in the availability of costly alternative therapies in multiple myeloma will enhance the role of economic evaluations in reimbursement decisions and amendments to the treatment guidelines. The quality of economic evaluations should be taken into account by clinicians involved in decision-making. A systematic review and critique of the methodology was performed to assess the trends and quality in economic evaluations in multiple myeloma to date. A literature search was conducted to identify full economic evaluations in multiple myeloma as of December 2009. Details of the economic evaluation methods applied were extracted. Each study underwent a quality assessment based on the Drummond checklist for appraisal of high-quality economic evaluations in health care. Eighteen published economic evaluations were identified. Stem cell transplantation in combination with intensive chemotherapy has been demonstrated to be cost-effective, while interferon alpha is generally ineffective at additional costs. Evaluations have become less frequent in the last decade, especially for newer therapies despite their important contribution to improvements in outcomes. The quality of the methodology applied and its documentation can be improved in many aspects. As users of the results of economic evaluations, clinicians involved in guiding decision-making should be critical of the quality of economic evaluations in multiple myeloma. To ensure access to and identification of high-quality studies, researchers conducting economic evaluations of future advances should strive towards evaluations that fulfil the Drummond criteria and are properly documented.

1. Introduction

Multiple myeloma is a progressive haematologic malignancy accounting for approximately 0.8% of all cancer diagnoses and 0.9% of all cancer deaths worldwide.[1] It is considered a severe disease which remains incurable.

The treatment paradigm for multiple myeloma usually consists of initial treatment which may include stem cell transplantation (SCT) followed by maintenance therapy to prolong patient response to initial therapy and treatment for relapsed or refractory disease. Supportive agents to alleviate symptoms of the disease or side-effects of treatment

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.04.005

are also commonly administered. Recently available novel therapies, such as thalidomide, bortezomib and lenalidomide, promise improved outcomes[2] at increased acquisition costs. Additional agents currently under development are expected to be added to the list of options available in the future.

Previous reviews of economic evaluations in multiple myeloma have found that economic evidence is scarce and largely lacking for novel therapies.[3,4] Earlier advances in treatment, such as SCT, resulted in higher incremental costs but led to relatively greater incremental effectiveness. More recent advances, however, have been shown to be marginally less cost-effective compared with earlier advances, despite being considered cost-effective. Accordingly, future treatments will likely become marginally less cost-effective, thus enhancing the role of cost-effectiveness studies in reimbursement decisions for multiple myeloma.

Continued expansion in the availability of costly alternative therapies will enhance the role of economic evaluations in reimbursement decisions and amendments to the treatment guidelines. To assess the validity of the results obtained from economic evaluations, the quality of the methodology applied to produce the results should be taken into account by users of their results. A critical review of the trends and quality of the methodology applied in economic evaluations in multiple myeloma has not been conducted. Therefore, the validity of the results reported by existing studies remains questionable to users of economic evaluations.

The objective of this review was to provide an overview of the trends in methodology. A critical appraisal of the methodology was also conducted to identify whether the quality was adequate for users of their results in decision-making and to identify needed improvements for future evaluations.

2. Methods

2.1. Search

A literature search was performed as of 31 December 2009 in Medline, EMBASE, and Cochrane Database of Systematic Reviews using the search strategy described in Appendix A.

2.1.1. Inclusion criteria

The following inclusion and exclusion criteria were used: (1) treatment for multiple myeloma was the main topic of the article; (2) only research articles were considered and abstracts and reviews were excluded after screening the references for relevant publications; and (3) only articles using the English language were considered. Full papers were obtained for publications whose titles or abstracts were considered relevant or where the title or abstract information was not sufficient to make a decision. Full papers were rejected if the article did not include both a costing and an effectiveness element to the study. Studies using data from a patient population heterogeneous for many types of diseases in addition to multiple myeloma were excluded if both cost and effect estimates specific to multiple myeloma patients were not reported.

2.2. Data extraction

Details of the economic evaluation methods applied were extracted, including the type of evaluation, comparators, source of data for effectiveness, time horizon, payer perspective, inclusion of indirect costs and discounting, effectiveness outcomes, and incremental costs and effectiveness. Source of funding for the study was also extracted.

2.3. Quality assessment

The criteria used for the quality assessment were based on Drummond's checklist, which is a standard quality assessment checklist specifically designed to critically assess economic evaluations.[5] It provides a list of ten general questions and accompanying sub-questions to assist users of economic evaluations in separating the various elements of methodology applied in economic evaluations so that each can be scrutinised. Questions 1 through 9 and all sub questions for criterion 10 were used (Table 1). Each of the questions was operationalised to enable a 'yes' or 'no' answer for each item on the checklist. If the article did not provide enough information to determine a clear answer to the question, the article was scored with a 'no' for the criterion in

Table 1 – List of criteria adapted from Drummond et al.[5] applied in quality assessment.

Q1	Was a well-defined question posed in answerable form?
Q2	Was a comprehensive description of the competing alternatives given?
Q3	Was the effectiveness of the programmes or services established?
Q4	Were all relevant costs/consequences for each alternative identified in light of viewpoint?
Q5	Were costs and consequences measured in appropriate physical units?
Q6	Were costs and consequences valued credibly?
Q7	Were costs and consequences adjusted for differential timing (i.e. discounted)?
Q8	Was an incremental analysis of costs and consequences of alternatives performed?
Q9	Was the impact of uncertainty in the estimates of costs and consequences examined?
Q10a	Was the conclusion easily interpretable and based on objective comparison in terms of costs and effect difference?
Q10b	Were the results compared with those of others and allowances made for methodological differences?
Q10c	Did the study discuss the generalisability of the results to other settings/patient groups?
Q10d	Did the study allude to or take account of other important factors in the choice or decision under consideration?
Q10e	Did the study discuss issues of implementation and whether freed resources could be redeployed to other programs?

question. If a criterion was met only for the costs or effects, this was also scored with a 'no' but made transparent.

3. Results

3.1. Search

Fig. 1 depicts the selection process conducted for this review. The search identified a total of 967 potentially relevant articles. After reviewing the titles and abstracts, 33 articles were selected for full review. Finally, we reviewed 18 studies that reported full economic evaluations, which included six cost-effectiveness analyses (CEA), five cost-minimisation analyses (CMA), three cost-utility analyses (CUA), three cost-benefit analyses (CBA) and one cost-consequence analysis (CCA). Of note, no CUAs have been conducted since 2004.

3.2. General characteristics of selected studies

All identified economic evaluations were published between the years 1994 and 2009. Details regarding the comparators and source of effectiveness are provided in Table 2. Details of the methodology are provided in Table 3.

3.2.1. Comparators and stage of treatment

An economic evaluation was found to be published for each stage in the treatment paradigm for multiple myeloma (Table 2). The majority of studies evaluated initial therapy, which consisted of conventional chemotherapy and/or stem cell transplant. Few have been published for targeted agents, with only one CEA conducted for bortezomib compared to best supportive care or thalidomide in the relapsed/refractory phase of treatment.

3.2.2. Data source for effectiveness

Effectiveness was demonstrated by a RCT ($n = 7$), retrospective cohort study ($n = 4$), and a meta-analysis of RCTs ($n = 3$). The study design applied to estimate effectiveness for the intervention and alternative comparators differed for five studies. The weakest comparisons were studies that compared effectiveness estimated from a RCT design to that of estimates from a retrospective cohort study[6] and a Delphi panel supplemented with estimates from the literature.[7] One study compared effectiveness estimated from a RCT to a meta-analysis that pooled estimates from both controlled and uncontrolled studies.[8] Two studies compared estimates from a prospective design to that from a retrospective design with both groups matched for patient characteristics to simulate a retrospective case-control study.[9,10]

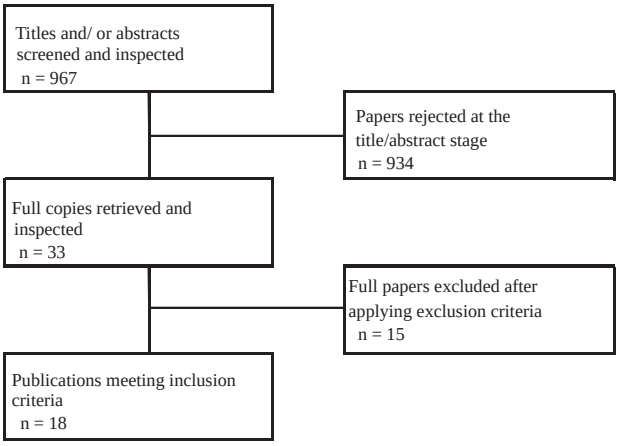

Fig. 1 – Flowchart describing the article selection process.

3.2.3. Perspective

The perspective was not stated for seven studies (Table 3). Perspectives that were stated included that of the payer, society, hospital and provider.

3.2.4. Time horizon and effectiveness outcomes

The time horizon varied between studies but was generally limited to the stage within the treatment paradigm. Evaluations of initial treatment most commonly adopted the longest time horizon and reported effectiveness outcomes in either life-years (LYs) or quality-adjusted life-years (QALYs). Studies assessing costs and benefits of SCT typically adopted a short time horizon since the objective of such analyses was to assess methods to save costs during the transplantation procedure. Consequently, effectiveness outcomes were reported in term of costs of treatment and adverse events. For maintenance and relapsed/refractory treatment, time horizons were either one year[11] or survival from start of treatment,[7,12] with effectiveness outcomes measures being months or LYs, respectively. Economic evaluations of supportive therapies assessed the costs and effects of treatment from one to three years and reported effectiveness outcomes in terms of monetary costs.[13–15]

3.2.5. Incremental cost and effectiveness

Most studies found the intervention to result in either improved or equal effectiveness compared to the alternative as well as increased costs. Some trends in incremental cost and effectiveness results can be seen. Transplantation alone or in combination with intensive therapy has generally been demonstrated to be effective though more costly.[6,9,10,16–19] The addition of interferon alpha (IFN) to therapy has generally been shown to be limited in terms of health outcomes while at additional costs,[8,12,20] with the exception of IFN in combination with VMPC (vincristine, melphalan, cyclophosphamide and prednisolone).[21] Cost-savings were demonstrated for outpatient versus inpatient transplants,[22] use of vincristine, adriamycin, dexamethasone (VAD) plus pegylated liposomal doxorubicin (DVd) instead of VAD plus low dose dexamethasone (VAd),[23] as well as large instead of standard volume leukapheresis collection when two transplants are required. Zoledronic acid for supportive care with bisphosphonates is as effective as pamidronate, though the incremental cost difference was not significantly different.[15]

3.2.6. Acknowledgement of funding

Variation in the source of funding was observed, with studies acknowledging either no funding, funding from the manufacturer, government and non-profit or academic organisations.

Table 2 – Comparator and source of effectiveness of published economic evaluations in multiple myeloma.

Study	Comparators		Stage of treatment	Intervention		Alternative		Source of effectiveness estimates (intervention/ alternative)	Sample size (intervention/ alternative)
	Intervention	Alternative		Data source	Sample size	Data source	Sample size		
Donatini et al. (1994)[19]	HDM + PBSCS[a]	Chemotherapy	Initial; Relapsed/ refractory	Retrospective analysis of a cohort study enrolling consecutive patients	16	Retrospective analysis of a cohort study enrolling consecutive patients	11	Retrospective cohort	16/11
Laakso et al. (1994)[14]	Clodronate	Placebo	Supportive	RCT	156	RCT	156	RCT	156/156
Henon et al. (1995)[16]	HDM + Auto-BMT (group I)[b]	M2 or VAD (group II and group III)[b]	Ititial	Retrospective chart review	12	Retrospective chart review	Group II: 10; Group III: 15	Retrospective cohort study	12/10 (group II); 15 (group III)
Duncan et al. (1996)[6]	ABMT	PBSCT	Transplant	RCT	14	Retrospective chart review	37	RCT/Retrospective cohort study	14/37
Jagannath et al. (1997)[22]	Outpatient tandem autotransplants	Inpatient tandem autotransplants	Transplant	Retrospective chart review	91	Retrospective chart review	160	Retrospective cohort study	91 / 160
Nord et al. (1997)[20]	MP-IFN	MP	Initial	RCT	285	RCT	298	RCT	285 / 298
Trippoli et al. (1997)[12]	IFN	None	Maintenance	Meta-analysis of 6 RCTs	393	Meta-analysis of 6 RCTs	423	Meta-analysis	393 / 423
Trippoli et al. (1998)[8]	ABMT	MP or MP+IFN	Initial	RCT	100	Meta-analysis of 4 controlled and uncontrolled trials	MP alone: 850; MP+IFN: 586	Meta-analysis of controlled and uncontrolled studies	100/850 (MP); 181 (MP+IFN)
Dranitsaris et al. (1999)[13]	Pamidronate	Placebo	Supportive	RCT	196	RCT	181	RCT	196/181
Ludwig et al. (2000)[11]	IFNa+VMCP	VMCP	Initial; Maintenance	Meta-analysis of 17 RCTs	1177 maintenance; 789	Meta-analysis of 17 RCTs	1156 maintenance; 826 initial	Meta-analysis	1,966/1,982
Gulbrandsen et al. (2001)[9]	HDM+ABSCS	MP	Initial	Prospective study	274	Retrospective cohort selected from an RCT to match characteristics of intervention group	70	Retrospective case-control study	274/70
Sampson et al. (2001)[17]	HDM + ABMT	Chemotherapy[a]	Initial	RCT	100	RCT	100	RCT	100/100
Kouroukis et al. (2003)[10]	VAD + ASCT	MP	Initial	Retrospective cohort selected by chart review to match characteristics of alternative group	36	RCT	16	Retrospective case-control study	36/16
Mehta et al. (2004)[7]	BMB (±previous Thal)	BSC or Thal	Relapse/ refractory	RCT	202	Delphi panel (supplement of literature for thalidomide)	Hypothetical cohort	RCT/Delphi panel	202/6[c]
Van Agthoven et al. (2004)[18]	Intensive M + myeloablative cyclo + ASCT	Intensive M	Initial	RCT	129	RCT	132	RCT	129/132
Reed et al. (2005)[15]	Zoledronic acid	Pamidronate	Supportive	RCT	151	RCT	138	RCT	151/138
Porter et al. (2007)[23]	DVd	VAd	Initial	RCT	97	RCT	95	RCT	97/95
Zubair et al. (2009)[24]	Large volume leukapheresis	Standard volume leukapheresis	Transplant	Retrospective chart review	35	Retrospective chart review	52	Retrospective cohort study	35/52

Abbreviations: ABMT: autologous bone marrow transplant; ABSCS: autologous blood stem cell support; ASCT: autologous peripheral stem cell transplantation; BMB: bortezomib; BSC: best supportive care; cyclo: cyclophosphamide; DR: Durie Salmon; DVd: vincristine, adriamycin, dexamethasone (VAD) plus pegylated liposomal doxorubicin; HDM: high-dose melphalan; IFN: interferon; M: melphalan; M2: BCMU (1,3 di[2-chloroethyl]-1-nitrosourea), vindesine, cyclophosphamide, melphalan; MP: melphalan prednisone; PBSCS: peripheral blood stem cell support; PBSCT: peripheral blood stem cell transplant; RCT: randomised controlled trial; Thal: thalidomide; VAd: VAD plus low dose dexamethasone; VMCP: vincristine, melphalan, cyclophosphamide and prednisolone.

[a] Standard chemotherapy consisting primarily of vindesine, adriamycin, prednisone, and carmustine.

[b] Group I patients of DS stage I, group II patients of DS stage I, group III patients of DS stage II.

[c] A total of six experts were surveyed to elicit effectiveness estimates based on a hypothetical cohort for whom the alternative would be administered.

Table 3 – Methodological characteristics of published economic evaluations in multiple myeloma.

Study	Type	Perspective (country)	Indirect costs	Time horizon	Discount rate	Effectiveness outcomes	Incremental Effects	Incremental Costs	Funding source
Donatini et al. (1994)[19]	CMA	Not stated (FRA)	None	6 years	Not done	OS QoL score	Equal	US$34465	None stated
Laakso et al. (1994)[14]	CBA	Not stated (FIN)	None	2 years	Not done	AEs	Included as costs	51 FM /day	Manufacturer Nonprofit Government
Henon et al. (1995)[16]	CEA	Not stated (FRA)	None	5 years	Not done	Weeks	Group I vs II: 138 weeks; Group I vs III: 20 weeks	Group I vs II: US$10,145; Group I vs. III: US$19,270	None stated
Duncan et al. (1996)[6]	CMA	Hospital (GBR)	None	Transplantation phase	NA	Inpatient hospital days AE-free days	Equal[a]	3,031£	Manufacturer
Jagannath et al. (1997)[22]	CMA	Not stated (USA)	Productivity loss	2 months	NA	AEs	Equal[a]	US$-13,172	Government
Nord et al. (1997)[20]	CUA	Societal (NOR, DNK, SWE)	Productivity loss	Death or censored	costs: 5%	QALYs	0.125 QALYs	NOK 87,600 (US$ 13,700)	Manufacturer
Trippoli et al. (1997)[12]	CMA	Not stated (ITA)	None	Lifetime	Not done	LYs	Equal	US$42,000	None stated
Trippoli et al. (1998)[8]	CEA	Societal (ITA)	None	Lifetime	costs: 5% effects: 5%	LYs	ABMT vs MP: 2.23 LYs; MP vs MP+IFN: Equal	ABMT vs MP: US$57, 333; MP vs MP+IFN: not done	None stated
Dranitsaris et al. (1999)[13]	CBA	Societal (CAN)	None	3 years	benefits: 3%	Risk of skeletal fracture AEs	Included as costs	Patient: WTP of Can$3,364; Society: Can$789	Manufacturer
Ludwig et al. (2000)[11]	CEA	Not stated (International)	None	1 year	NA	Months	Initial: 3.5 months; Maintenance: 7.6 months	Initial: US$161.33/wk; Maintenance: US$154.67/wk	Hospital
Gulbrandsen et al. (2001)[9]	CUA	Societal (NOR)	Productivity loss	3 years	costs: 5%	QALYs	1.2 QALYs	NOK 299,000 (US$ 32,300)	Nonprofit
Sampson et al. (2001)[17]	CEA	Provider (GBR)	None	5 years	Not done	LYs	0.7 LYs all patients; 0.8 LYs <60 years age;	10,480£	None Stated
Kouroukis et al. (2003)[10]	CEA	Payer (CAN)	None	Lifetime	costs: 5%; effects: 3%	Months	19.3 months	US$30,517	Nonprofit
Mehta et al. (2004)[7]	CEA	Payer (USA)	None	Lifetime	Not done	LYs	BMB vs BSC: 1.13 LYs; BMB[c] vs Thal: 1.1 LYs; BMB[d] vs Thal: 1.45 LYs	BMB vs BSC: US$50,797; BMB[c] vs Thal: US$54,777; BMB[d] vs Thal: US$31,551	Manufacturer

Van Agthoven et al. (2004)[18]	CUA	Hospital (NLD)	None	3 years	costs and effects: 4%	LYs QALYs	0.14LYs; 0.24QALYs	€13,067	None stated
Reed et al. (2005)[15]	CCA	Not stated (International)	None	13 months	NA	AEs	Equal	US$1,982[b]	Academic Manufacturer
Porter et al. (2007)[23]	CCA	Payer (USA)	None	Not stated	Not done	RR PFS OS	Equal	US-$1404	None stated
Zubair et al. (2009)[24]	CBA	Not stated (USA)	Productivity loss Transportation Accomodation	PBSC collection phase	NA	Relapse rate AEs	Included as costs	US$-7,497	Government

Abbreviations: AEs: adverse events; ABMT: autologous bone marrow transplant; BMB: bortezomib; BSC: best supportive care; EFS: event-free survival; IFN: interferon; LYs: life-years; M: melphalan; MP + IFN: melphalan prednisone plus interferon alpha; NA: not applicable; OS: overall survival; PBSC: peripheral blood stem cell; PFS: progression-free survival; QALYs: quality-adjusted life-years; QoL: quality of life; RR: risk ratio; Thal: thalidomide; WTP: willingness to pay.

[a] Validity of assumption is questionable.
[b] No significant difference.
[c] In patients previously treated with thalidomide.
[d] In patients not previously treated with thalidomide.

3.3. *Quality of selected studies*

Fig. 2 describes a summary of the quality of all studies included in this review according to the Drummond criteria. Details of the critique according to questions 1 through 9 and sub-questions for question 10 for each study are available in Appendix B and C, respectively.

Nine studies (50%) included a well-defined research question by stating somewhere in the article the objective of the analysis, comparator strategies and the perspective of the analysis.[6–10,13,17,18,20] Almost all studies (89%) clearly described the alternative given.[6–10,12–16,18–20,22–24]

Nine studies (50%) adequately demonstrated comparative effectiveness, mainly by means of a RCT or a meta-analysis of RCTs. The remaining studies demonstrated effectiveness of the comparator strategies by means of non-experimental comparisons.

Whether all relevant costs and consequences were identified (50%) and valued in appropriate units (56%) was difficult to determine for half of all studies. This was particularly a problem for studies that did not mention the perspective of the analysis.[11,12,14–16,19,22,24]

Nine studies (50%) valued both costs and consequences credibly,[9–11,13,15,16,18,20,23] while three did not provide enough information regarding the valuation procedure for costs in order to judge quality.[12,17,24] The remaining studies did not meet this criterion for a variety of reasons. One study compared post-therapy survival time between two groups for which time in therapy began at the start of therapy for the intervention while for the alternative follow-up began at the end administration of therapy.[19] An invalid assumption of equal effectiveness between comparator groups was assumed in one study[6] despite being shown to be statistically different and for another due to incomparable patient groups.[22] The validity of the cost analysis was questionable for one study which reported an insignificant difference in costs between the two comparator groups despite the significantly fewer costly side-effects reported in the trial.[14] A cost analysis assuming equal long-term costs for different comparator treatments and using cost estimates taken from a variety of country perspectives and institutions was considered invalid.[8] Lastly, the use of a Delphi panel to estimate the costs and effectiveness of the alternative strategy was not considered credible.[7]

Five studies (38%) did not incorporate discounting because the time horizon of the analysis did not extend beyond 1 year.[6,11,15,22,24] Of the thirteen studies with a time horizon greater than one year, three (23%) discounted both costs and consequences.[8,10,18] Only one of the three discounted health effects lower than costs to take into account the increase in future value of health.[10]

Twelve studies (67%) performed an incremental analysis of both costs and effects.[7–10,12,13,15–18,20,24] One study presented the incremental effectiveness between the alternative strategies but did not present the incremental costs.[22]

Studies that examined uncertainty in the cost and effect estimates did so by means of a sensitivity analysis. A total of ten studies (56%) performed a sensitivity analysis on predetermined parameters expected to have an impact on the results.[6–10,13,15,17,18,20]

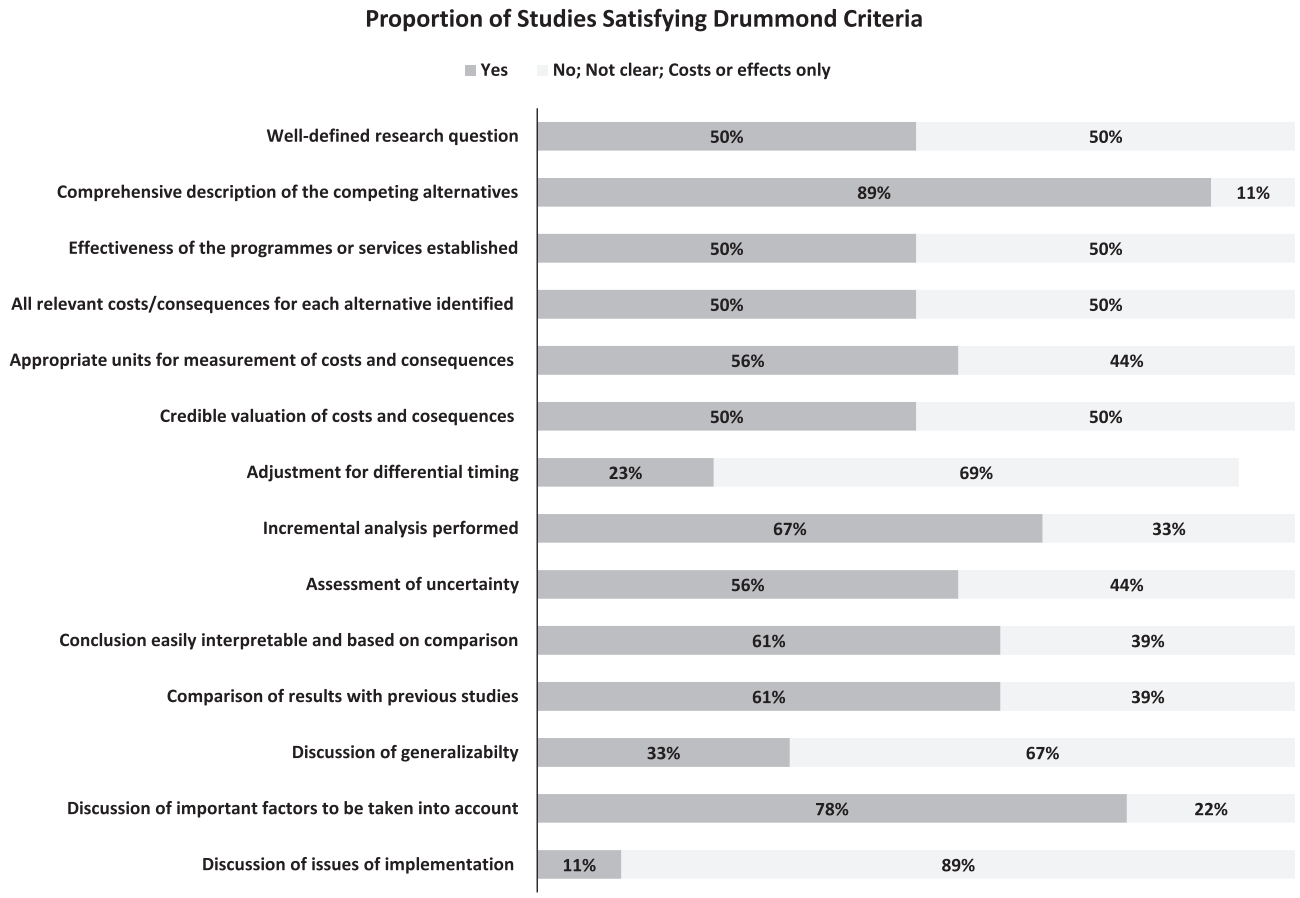

Fig. 2 – Summary of quality according to Drummond criteria.

Eleven studies (61%) based the conclusions on the interpretation of some overall index or ratio of costs to effectiveness, such as an incremental cost-effectiveness ratio (ICER).[7–10,12,13,16–20]

Eleven studies (61%) compared the costs and effectiveness results from their study to those of previous studies.[6,9,10,13,14,16–18,20,22,24] In some cases, the authors mentioned that there were no previous studies for comparison[13,18] or made comparisons to previous studies of other indications or treatments than that under study in the analysis.[8]

Discussion of generalisability was considered in six studies (33%).[8,10,13,16,18,23] The majority of these studies questioned the generalisability of the results to other patient groups or health care settings, namely due to differences in care and prognosis amongst patients in the source population compared to that in the study population.

Most studies (78%) took into account other important factors in the choice of decision under consideration, with four excluding a discussion of such considerations.[6,12,16,22] Important factors included improved protocol,[7,10,11,19] the addition of or a more precise estimate for costs,[10,13,17,23] and administration of treatment as an outpatient procedure or at home instead of as an inpatient,[18] end of patent and reduction of time required for infusion of treatment,[15] reduction in treatment-related risk for adverse events[24] and the difference in various patient subgroups.[14,20] Two studies stated that a more relevant comparator for the alternative strategy should have been used.[8,9]

Very few studies (11%) discussed issues of implementation.[16,22] Neither of the two studies that reported cost-savings with the intervention strategy[23,24] discussed whether freed resources could be deployed to other worthwhile programmes.

4. Discussion

Economic evaluations in multiple myeloma have become less frequent in the past decade. As of December 2009, two have become available in the literature since the latest review conducted by Moeremans and Annemans.[4] The past decade has also been marked by few CUAs in this indication, suggesting that a limitation persists in identifying treatment- and/or disease stage-specific utility values.

Evaluations of newer, advanced therapies such as thalidomide, bortezomib and lenalidomide are lacking despite their important contribution to improvements in survival and quality of life.[25] This suggests that evaluations of treatment for multiple myeloma are not keeping pace with the rate of advances in therapy. Given the continued expansion in the availability of alternative therapies as well as combinations of new and existing therapies, the number of economic evaluations in the indication of multiple myeloma should increase. Further advances in understanding the genomics of multiple myeloma are anticipated to further individualise treatment approaches for patients[26], resulting in much

needed assessments into whether an individualised approach leads to improved outcomes and cost-savings. Future analyses should also assess the added value of a drug in consideration of the sequence of all drugs between diagnosis and death. Such evaluations will be useful in formulating evidence-based guidelines for multiple myeloma in an era characterised by numerous alternative agents.

The quality of economic evaluations in multiple myeloma can be improved. The ability to judge the quality was often difficult because of inadequate description of the analysis, particularly for costs. It was unclear whether this was a result of poor quality in the methodology or documentation. Few studies incorporated standard methods expected in high-quality economic evaluations of healthcare, such as assessment of uncertainty in the estimates and discounting. Many studies relied on effectiveness estimates from non-experimental studies which were often based on different patient populations. The uncommon discussion of generalisability and issues of implementation is surprising given their importance for users of the results of economic evaluations. Discussion of generalisability allows users to consider issues of transferability of the results their setting. Further, to assess the feasibility of implementation and redeployment of newer yet more expensive treatment, it is important to discuss any changes in the administration of care and the associated acquisition costs.

Low transparency and methodological weaknesses in economic evaluations in the indication of haematology have been reported previously.[27,28] Weaknesses in methodology and documentation have also been reported in critical reviews of oncology treatment, such as colorectal[29,30] and breast cancer.[31,32] Poor quality may not be unique to haematology but more generally a hallmark of economic evaluations in oncology. As recent evidence has demonstrated that healthcare targeting more severe diseases is more likely to be reimbursed,[33] the trend for methodological weaknesses and low transparency of the results for economic evaluations in cancer treatment may suggest that disease severity leads to different requirements for methodology. Hence, quality may be overlooked in economic evaluations within oncology. With typically a high-cost per QALY threshold in oncology treatment, we argue that the highest quality possible should be required when incorporating the results of economic evaluations in decision-making.

This critical review has implications for those conducting economic evaluations of treatment for multiple myeloma. To ensure that high-quality studies are performed, improvements in documentation of the viewpoint and research question being addressed are necessary. A discussion of the generalisability of the results to other settings is also necessary. Standard methodology should be incorporated, such as discounting and sensitivity analyses, especially given the uncertainty surrounding estimates based on small number of patients and potentially incomparable groups. Lastly, there is a need for more research demonstrating the differences, or absence, therefore, in the quality of life of multiple myeloma patients so that utilities can be incorporated into a CUA. This will be necessary for assessment of newer, more expensive drugs that may provide smaller margins of improved effectiveness but a meaningful gain in quality of life.

A limitation of this study is the restriction to peer-reviewed articles. Due to the exclusion of conference abstracts, more recent economic evaluations of newer, more advanced therapies for multiple myeloma may have been discarded. However, the assessment of the quality of such studies is difficult due to the limited information provided in abstracts.

As advances in treatment of multiple myeloma are expected to continue, researchers conducting economic evaluations of advances in therapy as well as users of the results should take into account the implications of this critical review. Users should be aware that the quality of such studies varies. To identify economic evaluations for which the results

Table 4 – Critique of selected studies according to criteria 1 through 9 of Drummond et al.[5]

First author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Donatini et al.[19]	No	Yes	No	Viewpoint not clear	Viewpoint not clear	Costs only	No	No	No
Laakso et al.[14]	No	Yes	Yes	Viewpoint not clear	Effects only	Effects only	No	No	No
Henon et al.[16]	No	Yes	No	Viewpoint not clear	Viewpoint not clear	Yes	No	Yes	No
Duncan et al.[6]	Yes	Yes	No	Yes	Yes	Costs only	Irrelevant	No	Yes
Jagannath et al.[22]	No	Yes	No	Viewpoint not clear	Viewpoint not clear	Costs only	Irrelevant	Costs only	No
Nord et al.[20]	Yes	Yes	Yes	Yes	Yes	Yes	Costs only	Yes	Yes
Trippoli et al.[12]	No	Yes	Yes	Viewpoint not clear	Effects only	Effects only	No	Yes	No
Trippoli et al.[8]	Yes	Yes	no	Yes	Yes	Effects only	Yes	Yes	Yes
Dranitsaris et al.[13]	Yes	Yes	Yes	No	No	Yes	Effects only	Yes	Yes
Ludwig et al.[11]	No	No	Yes	Viewpoint not clear	Viewpoint not clear	Yes	Irrelevant	No	No
Gulbrandsen et al.[9]	Yes	Yes	No	Yes	Yes	Yes	Costs only	Yes	Yes
Sampson et al.[17]	Yes	No	Yes	Yes	Yes	Effects only	No	Yes	Yes
Kouroukis et al.[10]	Yes	Yes	No	Yes	Yes	Yes	Yes[a]	Yes	Yes
Mehta et al.[7]	Yes	Yes	No	Yes	Yes	Costs only	No	Yes	Yes
Van Agthoven et al.[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reed et al.[15]	No	Yes	Yes	Viewpoint not clear	Yes	Yes	Irrelevant	Yes	Yes
Porter et al.[23]	No	Yes	Yes	Yes	Yes	Yes	No	No	No
Zubair et al.[24]	No	Yes	No	Viewpoint not clear	Effects only	Effects only	Irrelevant	Yes	No
Total 'yes'	50%	89%	50%	50%	56%	50%	23%	67%	56%

[a] Discounting was examined in the sensitivity analysis.

Table 5 – Critique of selected studies according to subquestions for criteria 10 of Drummond et al.[5]

First author	Q10a	Q10b	Q10c	Q10d	Q10e
Donatini et al.[19]	Yes	No	No	Yes	No
Laakso et al.[14]	No	Yes	No	Yes	No
Henon et al.[16]	Yes	Yes	Yes	No	Yes
Duncan et al.[6]	No	Yes	No	No	No
Jagannath et al.[22]	No	Yes	No	No	Yes
Nord et al.[20]	Yes	Yes	No	Yes	No
Trippoli et al.[12]	Yes	No	No	No	No
Trippoli et al.[8]	Yes	No	Yes	Yes	No
Dranitsaris et al.[13]	Yes	Yes	Yes	Yes	No
Ludwig et al.[11]	No	Effects only	No	Yes	No
Gulbrandsen et al.[9]	Yes	Yes	No	Yes	No
Sampson et al.[17]	Yes	Yes	No	Yes	No
Kouroukis et al.[10]	Yes	Yes	Yes	Yes	No
Mehta et al.[7]	Yes	No	No	Yes	No
Van Agthoven et al.[18]	Yes	Yes	Yes	Yes	No
Reed et al.[15]	No	No	No	Yes	No
Porter et al.[23]	No	Yes	Yes	Yes	No
Zubair et al.[24]	No	Effects only	No	Yes	No
Total 'yes'	61%	61%	33%	78%	11%

can be useful for decision-making, the Drummond criteria are useful for judgment of quality. For researchers conducting economic evaluations, it should be realistic to satisfy each of the Drummond criteria. Consideration of the weaknesses reported here will ensure that reimbursement decisions and treatment decisions are based on the highest quality pharmacoeconomic evidence. If the trends in quality continue, the results of economic evaluations for decision-making will be of little value.

Conflict of interest statement

None declared.

Appendix A

Search strategy

The following search strategy was used in all databases to find relevant articles. Search terms 1 to 3 were used to identify studies involving multiple myeloma patients. Terms 4 to 18 were used to find economic evaluations. Lastly, the results from these three categories were combined in steps 19 to 21.

Search terms

1. Multiple myeloma*
2. Plasma cell myeloma*
3. Plasma-cell myeloma*
4. Economics
5. Econom*
6. Costs
7. Costly
8. Costing
9. Pharmacoeconomics
10. Pharmacoecon*
11. Budget*
12. Expenditure*
13. Energy
14. 12 not 13
15. 'Value for money'
16. Cost-eff*
17. Cost-ben*
18. Cost-util*
19. 1 or 2 or 3
20. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 14 or 15 or 16 or 17 or 18
21. 19 and 20

Appendix B

see Table 4.

Appendix C

See Table 5.

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