Advanced Cutaneous Malignant Melanoma: A Systematic Review of Economic and Quality-of-Life Studies

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ABSTRACT

Objective: Metastatic melanoma (MM), a major concern for health-care providers, is increasing. We systematically reviewed published articles describing the impact of interventions (drugs and screening) on quality of life (QoL) in patients with MM, and articles that measured QoL in MM. **Methods:** We searched secondary databases including MEDLINE, Embase, CINAHL, Cochrane, and DARE from inception to 2006 using MESH terms "melanoma" and "metastases." Economic articles were subject to established quality assessment procedures. **Results:** We found 13 QoL and five economic studies (three cost-effectiveness, two cost-utility; average quality = 83% ± 7%). No strong evidence was found in this review for cost-effectiveness of interferons in Canada (incremental cost-effectiveness ratio [ICER] = $55,090/quality-adjusted life-year) or temozolomide in the United States (ICER = $36,990/Life-year gained based on nonsignificant efficacy differences). Melanoma screening was not cost-effective in the United States ($150,000–931,000/life-saved) or Germany (no survival benefit). From the 13 QoL studies,

eight measured baseline QoL; six studied the same population, generating similar results using different approaches/outcomes. Tools used included GLQ-8, QLQ-C30, QLQ-36, QWB-SA, and SF-36. Baseline scores QoL scores ranged from 0.60 to 0.69. Another five studies (N = 959 patients) were randomized trials analyzing QoL in patients treated with dacarbazine alone, dacarbazine ± interferon, dacarbazine + fotemustine, interleukin ± histamine, and temozolomide. Little difference was found in QoL scores between drugs or between baseline and end point. **Conclusions:** Cost-effectiveness has not been widely demonstrated for treatment of MM. Only two studies with unimpressive results exist for treatments. Screening was not cost-effective in the United States or Germany. Generally, no significant improvements in QoL were found for any alternative for treating MM. A need exists for effective treatments that improve duration and QoL.

Keywords: advanced malignant melanoma, pharmacoeconomics, quality of life, systematic review.

Introduction

Melanoma is a major concern for health-care providers. In the United States, 22 out of 100,000 men and 14 out of 100,000 women are affected [1]. The incidence continues to increase globally, especially among fair skinned people, by 3% to 7% annually [1–3]. The increasing incidence of melanoma has also been associated with an increased mortality related to the disease, with attributable deaths totaling 7770 in 2005 [1]. The mortality rate for melanoma is especially remarkable for those presenting with the more severe forms (i.e., stage IV) of metastatic melanoma (MM). In those patients received a diagnosis of advanced MM, the median survival is approximately 6 months [4],

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with a 5-year survival of about 5% [5,6]. The poor prognosis associated with MM highlights the lack of an effective treatment regimen to combat the disease.

Although many agents have been studied in the treatment of MM, from immunotherapy with interferons and interleukins to combinations of chemotherapeutic agents, no one agent or strategy has demonstrated the consistent ability to induce a long lasting remission or substantially prolong survival [4]. As a result of the lack of an effective treatment, the main goal of treatment of MM is currently palliation. Therefore, MM treatments need to focus on improving the patient's quality of life (QoL). Additionally, given the poor outcomes, treatments should be carefully evaluated to determine their economic impact on payers and health-care budgets.

Although other systematic reviews have been done investigating the efficacy of different strategies for MM, to date there have been no systematic reviews that have examined the impact on the patient's QoL

not only of this disease but also of these systemic therapies used in its treatment. One study from Crott [7] reviewed two pharmacoeconomic analyses (i.e., one cost-effectiveness and one cost-utility) in cutaneous melanoma, in stages II and III, and in interferon-alpha as adjuvant therapy.

Therefore, we have performed a systematic review to examine all of the information published so far on the impact of interventions on QoL, including all available treatment strategies or screening programs for MM. In addition, we have also compiled all available QoL analyses to determine the state of the art and whether any specific strategies offer advantages over the others.

Methods

A comprehensive literature review was undertaken to identify all published reports that dealt with the economic impacts of MM or its treatment on the patient's QoL. The patients of interest are adults with metastatic disease, including stage III (nonresectable) or IV, as defined by the American Joint Committee on Cancer Staging [8].

The studies included in the review were reports of original research related to QoL in MM and/or economics of MM. Specifically, articles must have been published in a peer reviewed journal or referenced in one of the databases as outlined in the search strategy below. Studies were excluded from this analysis if the intervention studied involved surgery, resectable disease, or radiation therapy. Additionally, any studies that grouped different types of cancers together where subjects with MM could not be separated from others were also excluded. No restrictions were placed on the age of patient, language of publication, or the year of publication. Secondary databases used in the search strategy were MEDLINE, Embase, CINAHL, Cochrane, and DARE, all from inception to 2006.

The search strategy for all studies included the MESH heading "melanoma" combined with any of the following non-MESH headings: "metastasis," "metastatic," "disseminated." These results were then combined with a thorough list of MESH headings concerning economic analyses (i.e., cost analysis, cost-benefit analysis, cost control, cost savings, cost of illness, etc.) as well as non-MESH headings (i.e., "burden of illness," "cost of treatment"). Finally the resulting reference lists of all articles identified, as well as several review articles, and the author's personal files were checked for suitable articles. We did not search textbooks, the Internet, including Web sites of organizations (e.g., manufacturers, pharmaceutical associations, or cancer support groups), or sites reporting on professional meetings or symposia.

The search strategy was again performed to identify all articles potentially presenting QoL data. Nevertheless, instead of using the economic terms in the last portion of the search strategy the following terms were used: "quality of life," "quality adjusted life years," "health status," "QoL," and "QALY." Again, when MESH headings were not available, the term was searched as a keyword. Similarly, the reference lists of all articles identified, as well as several review articles, and the author's personal files were checked for suitable articles. QoL articles identified were divided into two subsections, the first to establish the baseline QoL for patients with MM, and the second to compare and contrast changes in QoL that may have been noted in randomized controlled trials of different therapies for MM.

Two independent reviewers performed the above search for both sections and selected all relevant articles as per the inclusion and exclusion criteria. Differences identified in the articles selected were resolved via consensus discussion or a fourth judge was recruited who made the final decision. Three independent reviewers carried out the systematic narrative review of all studies identified.

Each full economic analysis article (i.e., evaluating both costs and consequences in at least one drug and one comparator) included in the review was assessed for quality using the scale described by Iskedjian and colleagues [9]. The quality assessment checklist used in our study allowed a total possible score for each of 4 (range 0–4) for each of the 13 listed items. If an item was considered not applicable (NA), it was labeled as such and was not included in the calculation. Thus, articles could earn a score ranging from 0 to 52 points. To arrive at the final score for each article, the total number of points awarded was then divided by the number of pertinent questions. Final scores for articles therefore ranged from 0 to 4, and these article scores could be interpreted in a similar manner to the individual items. To express as a percentage, this total value was divided by 4.

Data are presented in a narrative manner, where we describe all relevant information regarding studies methods (i.e., study design, patients included in the study, type of analysis, outcome measurement, etc.), main results, and conclusions. We also discuss positive and negative points of the included studies. Specifically, information regarding QoL and economic data from the studies are summarized and included in two tables containing: first author, year of publication, patient demographics, disease characteristics, interventions, outcome measurements, and main outcomes (quantitatively).

Results and Discussion

Pharmacoeconomic Analyses

The systematic search identified 68 abstracts, which were reviewed for their relevance to the inclusion and

exclusion criteria. From those articles, a total of 11 were selected to be retrieved and their full text assessed. After review, we found five studies [10–14] that dealt specifically with metastatic cutaneous melanoma. Two of those articles [10,11] examined the cost-effectiveness of drugs and the other two [12–14] studied screening programs. The overall quality scores for the economic analyses was 84% ± 6%, which would be considered very well. Table 1 presents these studies and their characteristics.

In Canada, Crott and coworkers studied the cost-utility of adjuvant high-dose interferon alpha compared with no adjuvant treatment in cutaneous melanoma [10]. The authors used a Markov model with a hypothetical cohort of 1000 patients with stages II to III cutaneous melanoma as a starting point in the analysis. The model analyzed the first 7 years of survival and recurrence in those patients, and then extrapolated the results over a 35-year period using clinical data from a published trial. Costs included in the analysis included those for interferon treatment, follow-up care, and treatment of recurrences. Costs were presented in 2004 Canadian dollars (CAD $; currently CAD $1 = USD $0.85), and discounted in a 6% rate per year. Utility estimates were assessed by face-to-face interviews in pharmacies on a sample of 104 people from general population in the province of Québec, Canada, using time-trade-off method. Sensitivity analyses were performed for discount rates, and a Monte Carlo simulation for stochastic data using 1500 iterations.

Incremental costs of using interferon alpha as adjuvant therapy over no interferon alpha were CAD $2809 over 7 years, and CAD $2870 over 35 years for 100 patients. Incremental quality-adjusted life-years (QALYs) were 51 over 7 years, and 205 over 35 years. Incremental cost-effectiveness ratios (ICERs) were CAD $55,090 for the 7-year time horizon. Nevertheless, in a sensitivity analysis over 35 years (the life expectancy for a healthy Canadian without cancer), the ICER dropped to CAD $14,003. In sensitivity analyses, these estimates were noted to be unstable, being highly influenced by clinical and utility data, as well as the discount rates. The article's main results clearly fell into what would be accepted as a cost-effective therapy according to the Canadian Guidelines for economic evaluation of pharmaceuticals (i.e., ICERs of CAD $20,000–100,000 per QALY), described by the Canadian Agency for Drug and Technology Assessment (CADTH) [15].

The major limitation of that study was the quality of input data used in their model. The long-term disease-specific recurrence rate is a subject of debate, which can affect results dramatically. As well, utility values were obtained from different populations (i.e., clinical experts, early stage melanoma patients, and the general population). On the other hand, the total cost

estimates calculated in that study were similar to those from other published studies and appear to be cost-effective over the long-term. Nevertheless, one might debate the extrapolation of results over a time horizon of 35 years, which they used in a sensitivity analysis. It would be highly unlikely that all patients would live that long, considering that they all had metastatic cancer that is invariably fatal. Therefore, results should be interpreted while acknowledging these limitations.

The other pharmacoeconomic article by Hillner et al. [11] scored 3.4 out of 4 (86%) on the quality scale. They compared the use of the standard, dacarbazine, with a parallel prodrug, temozolomide. The major drawback of that study was that the results were based on a clinical trial that did not demonstrate a statistically significant difference between the two treatment arms being compared, which were dacarbazine (DTIC) and temozolomide. Based on the clinical trial, those authors performed a cost-effectiveness and cost-utility analysis.

They found that the cost to gain an additional year of life using temozolomide instead of dacarbazine was USD $36,990 dollars in 2000. As expected in a trial that did not show any statistical difference, the sensitivity analysis varied from dacarbazine being both cheaper (ICER = –$65,180/life-year gained) and more effective to use (i.e., dominant), to the cost of an additional year of life gained of USD $18,670. Thus, the majority of the ICERs in the 95% confidence interval actually favored dacarbazine.

Another major limitation of that study was that adverse effects were not taken into account. The pharmacoeconomic analysis was based on a nonsignificant difference in efficacy favoring temozolomide, yet inconsistent logic was applied because a similar increase in adverse effects favoring dacarbazine was disregarded. Finally, the additional year of life was based on time alive only, with no adjustment made for the quality of that life. Therefore, adjusting for QoL would be expected to have increased the cost-effectiveness ratio. Overall, that economic evaluation was well performed technically, however, its major limitation was that the results on which the analysis was based were are not significantly different, which calls into question the usefulness of the results presented.

Hoffmann et al. [13] examined a German cohort of 661 patients with cutaneous melanoma. They evaluated the performance, costs and survival benefits of various staging methods. Screening methods included history and physical examination (H & P), chest x-ray (CXR), sonography of the abdomen (SAB), and high resolution sonography of peripheral lymph nodes (LNS). Of all the patients followed from January 1983 to November 1999, only 93 had stage III disease. Data collected included survival status, diagnosis of

Table 1 Characteristics and main results of health economic analyses of interventions in advanced cutaneous metastatic melanoma

Author (year)	Country	Evaluation type	Disease stage	Quality score	Economic perspective	Alternatives compared	Outcomes	Type of costs	Currency	Main results
Agnese et al. (2003) [12]	US	CEA	NS	85%	Hospital	Sentinel lymph node biopsy only	Life saved	Physician fees, medications, and radioisotope and nuclear medicine departmental charges.	USD	The cost per life saved using sentinel lymph node biopsy is estimated to be $627,000 to $931,000.
Crott et al. (2004) [10]	Canada	CUA	II and III	88%	Ministry of Health	High-dose interferon alpha and observation only	QALYs	Drug costs, follow-up costs, and cost of a recurrence	CAD	Incremental cost/ QALY = $55,090. Cost-effectiveness of high-dose interferon in melanoma patients show acceptable ratio of $14,003 if long-term (35 years) survival is taken into account.
Hillner et al. (2000) [11]	US	CEA	III and IV	86%	Societal	Temozolomide and dacarbazine	Mean survival and life-years gained	Drug costs, durable costs, professional services, laboratory monitoring, nonmedical costs.	USD	Incremental cost/ Life-year gained = $36,990; benefits of temozolomide are in the range of other new adopted therapies.
Hoffmann et al. (2002) [13]	German	CEA	I, II, and III	73%	Ministry of Health	Staging screening methods	Efficacy rate in detecting metastases	Costs of imaging procedures and costs caused by false-positive results	Euros	The cost-effectiveness ratio was best at initial staging and the follow up in stage III. Screening had no impact on survival.
Mooney et al. (1997) [14]	US	CEA + CUA	All	87%	NS	Lifelong screening vs. no screening	Life-years gained, QALYs	X-ray, CT scan, thoracotomy	USD	Incremental cost/life-year = $150,000, per QALY = $165,000. Discounting increased all costs

CAD, Canadian dollars; CEA, cost-effectiveness analysis; COI, cost of illness; CUA, cost-utility analysis; NA, not applicable; NS, not stated; QALY, quality-adjusted life-years; USD, United States dollars.

synchronous or metachronous secondary MM or other cutaneous malignancies, and time points of each physical examination/diagnostic imaging procedure at initial staging during follow-up. Patients with stage III cutaneous melanoma were followed for a median of 1.5 years.

Costs of follow-up at clinical stages were calculated in year 2000 Euros (€; currently, €1 = USD $1.29). Costs of routine methods for stage III patients and detection rates of metastases were: H & P €46,840 and 51.7%; CXR €8135 and 5.0%; SAB €10,764 and 1.6%; and LNS €22,209 and 10.0%, respectively. Because the main focus of that study was to evaluate the cost-effectiveness of screening methods to detect metastasis during initial cutaneous melanoma staging, there was little discussion of follow-up during stage III cancer. Even though the data suggest superiority for a particular screening method, no further analysis was performed (e.g., incremental cost-effectiveness analysis), neither for the initial stages nor for advanced cutaneous melanoma. The quality score was 2.9 (73%).

In the United States, Agnese et al. [12] examined data from 138 patients in a melanoma database during 1994 to 2002 who underwent sentinel lymph node biopsy for thin melanomas. Their objective was to determine the cost-effectiveness of that procedure in terms of patient survival. In theory, biopsy should enable practitioners to identify early those patients who might benefit from surgical intervention (i.e., lymphadenectomy) and chemotherapy. Costs were collected for physician care (surgeon, radiologist, and anesthesiologist), drugs (antibiotics, analgesics, dyes, and anesthetics), nuclear medicine, pathology, and room costs (operating room, recovery, ambulatory care). Costs were compared with a similar sized group who received wide excision as outpatients. Survival was noted in all cases.

These authors found that there was no difference in survival, because the overall rate was 98.6% for all patients. Patient charges averaged $12,193 (range: $10,096–15,223) as compared with $1466 (range: $1000–1740) for wide excision. Thus, biopsy was dominated by wide excision. If all patients died, the total cost per life saved would be between $627,000 and $931,000. These authors called into question the practice of using this technique in patients with thin melanomas.

In the final economic analysis, Mooney et al. [14] used a hypothetical cohort of American patients diagnosed in 1996 with tumors of intermediate thickness. They used a Markov model to examine the benefit of screening over the patient's lifetime to determine the cost-effectiveness of lifelong screening versus no screening these patients. They relied on local data from their cancer database and the literature for inputs into the model, which had a time horizon of 20 years.

The screening program cost $28.9 million over 20 years and produced an additional 193 life-years (175 QALYs). That amounted to an additional 8 months of life gained (0.6 QALYs). The incremental cost was $150,000/life-year and $165,000/QALY gained, which rose to $199,000 and $215,000, respectively, with 3% discounting of costs. When benefits were also discounted, the ICERs rose to $220,000 per life-year and $240,000/QALY, respectively. They did find that costs decreased substantially with decreased intensity of screening. Thus, their final conclusion was that lifelong screening for intermediate-thickness melanoma was not cost-effective.

One of the limitations of this review was the very small number of economic studies. There were only two that examined drugs [10,11] and three that examined screening [12–14]. As well, not all patients in all studies had very advanced disease. Therefore, results are based on a relatively small sample of patients. Thus, more research is needed to discover newer, more effective treatments that extend life and increase QoL for patients.

Another limitation was that our focus was on advanced disease, which tends to be the most expensive to treat. Therefore, future research could be directed at the earlier phases of the disease (i.e., stages I and II) or stage III disease that was not widely disseminated (e.g., only locally advanced). As well, we omitted studies of resected melanomas, on which trials have been done; however, no reviews were found having that focus. Because those patients differ in terms of disease progression and prognosis, such a review would be warranted. A further area that merits attention is disease prevention. No articles were found in this review that addressed this very important issue. This is especially true for MM, which is curable in its early stages, but fatal when it progresses to MM.

Quality of Life

The initial search identified 415 abstracts that were reviewed. From these, 33 full text articles were examined more closely to determine their suitability for the stated objectives. Eight articles met the criteria for this analysis. In addition, five other references were added from a review of their references for a total of 13 articles to be reviewed here [16–28]. Table 2 provides the details of these studies. There were six studies that used survey methods to obtain longitudinal data from patients [17,18,24–27] and seven that were based on clinical trials [16,17,20–23,28].

Four of the six accepted survey-based articles concerned the same study of a single group patients [24–27]. In the initial analysis, a group of patients (N = 89) was enrolled who were deemed eligible for a clinical trial comparing dacarbazine and vindesine or those two drugs in combination with cisplatin [24]. Not all patients who participated in the QoL analysis

Table 2 Characteristics and main results of published quality-of-life studies in advanced cutaneous metastatic melanoma

First author (year)	Country	Study design	Follow-up period	Patients	Interventions	Clinical outcome	Adverse events	Quality of life instruments	Main quality of life results
Avril (2004) [16]	Multinational	RCT	Until the end of the induction period	156 patients with disseminated malignant melanoma	Fotemustine and DTIC	OR: FOT = 15.2%, DTIC = 6.8% (P = 0.043) MS: fotemustine = 7.3 months, dacarbazine = 5.6 months	NP: FOT = 51%, DTIC = 5%; TC: FOT = 43%, DTIC = 6%	EORTC, QLQ C30	Global Health Status declined from 64 ± 2.6 at baseline to 62 after treatment in fotemustine group but remained at 64 in dacarbazine group before and after (difference = NS).
Beusterien (2003) [17]	US	RCT	4 months	301 patients with metastatic melanoma	Histamine dihydrochloride + IL-2 and IL-2 alone	MS: IL2 = 74.3 days; IL2 + histamine = 105.6 days (P = 0.007)	NR	QWB-SA	Overall quality of life increased from a baseline of 73.4 ± 1.9–80.5 ± 3.4 after interleukin plus histamine and from 70.9 ± 1.9 to 82.5 ± 4.4 with interleukin alone (difference = NS). QoL scores deteriorated more quickly over time in the IL-2 alone group.
Brown (2000) [18]	Australia	Longitudinal survey	Up to 2 years	91 patients with distant metastases and 19 with primary melanoma	NR	N/A	N/A	Linear analog self-assessment scale including the GLQ-8	Among QoL indicators, only tiredness correlated significantly (P < 0.001) with psychological adjustment in the last year of life. There was some deterioration in psychological adjustment.
Butow (1999) [19]	Australia	Longitudinal survey	3 months–2 years	125 patients with metastatic melanoma	NR	N/A	N/A	GLQ-8	GLQ-8 and PACIS scores were highly correlated (0.62). The psychological variables of perceived aim of treatment, minimization, and anger were independently positively predictive of survival.

Study	Country	Study type	Follow-up	Patients	Intervention	Survival/response	Toxicity	QoL instrument	Results
Coates (1993) [20]	Australia	RCT	NR	152 patients with metastatic malignant melanoma	DTIC and DTIC + IFN-alpha2a	OR: DTIC = 21%, DTIC + IFN2 = 17% (P = NS); MS: DTIC, DTIC + IFN2 = 229 days, DTIC + IFN2 = 269 days (P = NS)	Toxicity worse with DTIC + IFN2	Linear analog self assessment scale including GLQ-8	GLQ-8 median = 124, QL = 6. All of the quality of life scores measured were significant predictors of subsequent survival.
Cohen (2002) [21]	US	CT	Up to 2 months	30 patients with advanced stage III and IV malignant melanoma	Heatshock protein peptide complex 96 tumor vaccine	NR	NR	SF-36	Melanoma patients reported similar QoL to patients with metastatic renal cell carcinoma who received the same treatment, similar QoL to patients with type II diabetes and significantly better QoL than patients with congestive heart failure. Baseline General Health perceptions increased from 59 ± 21 at baseline to 60 ± 21 after treatment, compared with 72 ± 20 in the general population.
Kiebert (2003) [22]	UK	RCT	Up to 24 weeks	305 patients with advanced metastatic melanoma	TEM and DTIC	MS: TEM = 1.9 months, DTIC = 1.5 months (P = NS)	TEM = 33 Grade 3 or 4 events in 156 patients, DTIC = 33 events in 159 patients (P = NS)	EORTC, QLQ C30	No significant differences for global QoL were found in both interventions in weeks 12 and 24 after randomization.
Ridolfi (2002) [23]	Italy	RCT	18 months (median)	176 patients with advanced melanoma	CIS and DTIC with or without IL-2, and iIFN-alfa-2b	MS: CIS + DTIC = 9.5 months, CIS + DTIC + IL2 = 11.0 months (P = 0.51); OS: 20.2% and 25.3%, respectively (P = 0.70)	63 Grade 3 or 4 events in 89 CIS + DTIC patients, 95 in 87 patients on CIS + DTIC + IL2	Rotterdam Checklist Symptom questionnaire	NR
Sigurðardottir (1993) [24]	Sweden	Longitudinal survey	9–12 weeks	43 patients with generalized malignant melanoma	DTIC + vindesine and DTIC + vindesine + CIS	N/A	N/A	EORTC QLQ-36	Mean difference of global quality of life scores between patients and their relatives were −11.5 (SD = 23.5) and −3.5 (SD = 24.0) at 9 and 12 weeks, respectively.

Table 2 continued

First author (year)	Country	Study design	Follow-up period	Patients	Interventions	Clinical outcome	Adverse events	Quality of life instruments	Main quality of life results
Sigurðardottir (1995) [25]	Sweden	Longitudinal survey	8–12 weeks	95 patients with generalized malignant melanoma	DTIC + vindesine and DTIC + vindesine + CIS	N/A	N/A	Questionnaire addressing opinions on chemotherapy and ethical conflicts	50% of the patients reported that treatment had been helpful and very few had thought about stopping the treatment
Sigurðardottir (1996) [26]	Sweden	Longitudinal survey	9–12 weeks	52 patients with generalized malignant melanoma	DTIC + vindesine and DTIC + vindesine + CIS	N/A	N/A	EORTC QLQ-36	Global health/quality of life scores after treatment were 63.7 (SD = 23.7). After 9 weeks of follow-up, this mean score dropped to 49.5 (SD = 21.3)
Sigurðardottir (1996) [27]	Sweden	Longitudinal survey	9–12 weeks	89 patients with generalized malignant melanoma	DTIC + vindesine and DTIC + vindesine + CIS	N/A	N/A	EORTC QLQ-36	During pretreatment phase, patients global health/quality of life mean scores were 69.3 (SD = 23.7)
Young (2001) [28]	UK	RCT	Up to 52 months	61 patients with metastatic melanoma	DTIC alone and DTIC + IFN-alpha	MS: DTIC = 7.2 months, DTIC + IFN = 4.8 months ($P = 0.91$ after adjustment); 6-month survival: DTIC = 58%, DTIC + IFN = 40% ($P = $ NS)	DTIC: 23 Grade 3 events in 31 patients; DTIC + IFN = 30 Grade 3 events in 30 patients; All patients died.	EORTC, QLQ C30	Overall there were no significant differences in QoL between the two treatment arms, both at baseline and for the change in scores over time (actual scores not given).

CIS, cisplatin; CT, clinical trial; DTIC, dacarbazine; EORTC, European Organization for Research and Treatment of Cancer; FOT, fotemustine; GQL-8, a multi-item quality of life visual analog scale scoring from 0 to 474; IFN, interferon; IL, interleukin; MS, median survival; N/A, not applicable (not a clinical trial); NP, Grade 3 or 4 neutropenia; NR, not reported; NS, not significant; OR, overall response (complete + partial response); OS, overall survival; PACIS, Perceived Ability to Cope with Illness Scale; QL, Quality of Life Index (5–14 scale); QLQ, Quality of Life Questionnaire; QoL, quality of life; QWB-SA, Quality of Well-Being Scale self-administered; RCT, randomized clinical trial; SF, short-form; TC, Grade 3 or 4 thrombocytopenia; TEM, temozolomide.

were enrolled into the trial (N = 22 not enrolled) and, as a result, the analysis of the patients was as a whole and not by the specific treatment arms into which they had been randomized.

All patients were given the European Organization Research and Treatment of Cancer (EORTC) core questionnaire in an effort to validate it for patients with MM. In addition, subjects also completed a study-specific module for MM similar to the EORTC quality of life scale (QLQ-C36) and a Hospital Anxiety and Depression scale. In that report, it was noted that the completion of the form caused patients little distress and only took 15–20 min. These patients were a group with relatively low symptom burden and few physical symptoms. More importantly for QoL research purposes, the QLQ-C36 was noted to have had construct validity and reliability, with the exception of role functioning and nausea and vomiting symptom subscales, as determined by a group of a priori standards. As well, it was applicable to use in patients with generalized MM.

The second publication [25] contained data that were represented in other publications and therefore will not be summarized here. The next portion of the trial [26] examined the long-term follow up of the patients at 9 weeks, which was 1 week after their scheduled third cycle of chemotherapy. This time period was thought to coincide with the maximum point of adverse effects. During that analysis, the authors noted that there was a high number of dropouts as a result of patients' experiencing progressive disease or death. These drop outs were noted to have occurred earlier and faster than in comparable studies of lung, breast, and colorectal cancer. Of those patients who did complete the QLQ-C36, a significant deterioration of all of but one of the functioning subscales (i.e., emotional) and an increase in all of the symptom subscales except for the one discussing pain. Similarly, the global health/QoL subscale also worsened. Interestingly, the group that was not entered into the trial had the least deterioration. Reasons for the slower deterioration were not given in the article. Of those patients entered into the trial, the only differences that could be identified were predictable based on the medications being administered. Those in the arm that were treated with the high intensity regimen containing cisplatin had an increase in their symptom scales associated with their hearing, nausea and vomiting, appetite and a non significant decrease in their role functioning. The one surprising aspect was that patients in the other chemotherapy group had an increase in their neurological symptoms. Finally, in this part of the trial, it was noted that the physician-rated outcome variables did not correspond to the patients' measured QoL and it was concluded that the physicians' assessment of QoL in this form was a poor approximation of a patient's true QoL.

Similarly, in the last analysis on these groups of patients [27], the patients' reports of QoL were compared with that of their next of kin at week 12 of therapy and nurses' assessments at week 9 of therapy. Both of these new groups completed a form similar to the QLQ-C36. For the relative portion, there were a total of 34 matched pairs of patient-relatives. It was noted that there were no statistical differences between the responses of the patients and those of the relatives.

This finding was in stark contrast to the nursing assessment. It was found that the nurses more often underestimated a number of items such as the patient's fatigue and difficulty in concentrating. Also, the nurses tended to overestimate the degree of nausea and vomiting as well as the patients' global QoL. Several reasons for this disparity were proposed: that the nurses were not trained in assessing these types of items, the nurses were not trained in the use of the instrument, the nurses expressed difficulty in answering all of the questions on the form (such as the impact of the disease on the person financially), and that the patient's relatives had a longstanding history of what the patient's function was prior to the treatment and how they were currently feeling.

In summary, these four publications found that the QLQ-C36 developed by the EORTC was a valid tool for assessing the QoL in patients with MM. As well, it also highlighted that QoL, when using this tool especially, is best performed by the patient or a close relative rather than by a health-care provider. Finally, these studies revealed the tremendous burden experienced by patients with MM highlighted by the general decline in functional domains as well an increase in symptoms. This increase in symptoms may be associated with the types of chemotherapy being used.

The next two articles [18,19] concerned a group of 125 patients seen for the first time for their treatment of MM. The patients included in the trial differed slightly from those who could have been included into the trial, but declined to participate. Those not participating more often had liver or brain metastases. The increased morbidity was reflected in a median duration of survival of 299 days in those patients included in the analysis and only 138 days in those not participating.

In the analysis by Butow [19], patients completed the "GLQ-8" linear analog self-assessment scale, which measured eight physical and emotional domains. They also filled out the Perceived Ability to Cope with Illness Scale (PACIS), which is a single item scale that assesses the patient's ability to cope. Both scales were scored from 1 to 100 where higher scores reflected a better prognosis. The GLQ-8 scores were summed for a possible patient score that could range from 8 to 800. When those patients were followed up, it was noted that both of these scores were positively associated with the patient's length of survival. Nevertheless, the hazard ratio and associated 95% confi-

dence interval were very small: GLQ-8: 0.99 (0.992–0.996), and PACIS: 0.992 (0.985–0.999). These results reflect that those patients with a higher QoL have a better chance for survival. The authors suggested that when designing clinical trials in MM, the study should attempt to control for QoL at baseline because not doing so may cause a bias in the results.

The second study of this group of patients examined only a portion of the individuals in the initial trial [18]. Ninety-one of the patients were found to have several of their QoL indicators (e.g., feeling sick, tiredness, physical well being, appetite) associated with the "patients' ability to minimize the impact of their cancer." The authors gave the following example to illustrate the utility of the analysis, "Patients who minimized the impact their cancer, and expressed low levels of anger were likely to have better indicators of QoL." Nevertheless, the opposite cannot be concluded from that trial, that by changing patients' QoL it will affect the impact the cancer has on their lives.

The last baseline analysis of QoL [21] examined 31 patients undergoing a Phase 1b study of a heat shock protein peptide complex 96 (HSPPC-96) autologous tumor vaccine treatment. These patients all had stage III or IV disease, but had a life expectancy longer than 4 months. Thirty patients completed the SF-36, a tool with eight subscales ranked 0 to 100 with 100 indicating the best QoL on that given item. Similarly, the patient's physician completed a Physician Component Summary (PCS), which was similar to the SF-36. The QoL forms were completed at baseline, 3 weeks later when patients were receiving the 4th and final treatment and 1 month after completing the treatment. Throughout the follow up, there were no significant differences in any of the scores calculated indicating that the vaccine did not negatively affect the patient's QoL. Nevertheless, when the results of the SF-36 were compared with those from a group of historical patients with other illnesses, it was noted that the patients with MM had a similar QoL to patients with Type II diabetes, a worse QoL than the general population (in the domains of physical function, role limitation, bodily pain, and general health perception), and had a better QoL than patients with heart failure (in the domains of general health and vitality).

Six randomized controlled trials compared the QoL experienced in the patients as part of their analysis [16,17,20,22,23,28]. Unfortunately, although designed for this purpose, the trial by Ridofi et al. [23] did not report the QoL results and no companion paper could be found, despite a thorough search. The authors reported no significances in the clinical outcomes that they examined between patient groups.

Another trial by Kiebert [22] had the QoL results in one paper and clinical results published in a companion paper [29]. In that trial, patients were randomized to either dacarbazine or temozolomide. They did not find a statistically significant difference between the groups in terms of overall survival or response to therapy based on complete or partial remissions [22,29]. The QoL analysis performed was also noted to be missing a number of patients during the analysis. Of the 305 patients randomized in the trial, only 110 completed the EORTC QLQ-C30 at baseline. The lack of data continued at week 12 where only 31 patients in the dacarbazine arm and 50 patients in the temozolomide arm completed the QoL analysis. As expected, the dropout rate was even higher at 24 weeks with only 30 patients in total completing the QoL assessment Although the numbers were small and conclusions about the effect of the drug on QoL are difficult to make, at 12 weeks those patients randomized to temozolomide were noted to have a statistically significantly better response on the physical function subscale as well as less fatigue and sleep disturbance on the symptom subscale. Overall, however, there was no significant difference between groups.

Another trial that used the EORTC QLQ-C30 to assess the QoL was in a trial comparing dacarbazine with or without interferon [28]. Similar to the trial previously discussed, there was a poor response in adherence to the QoL tool. Only 38 of the 61 patients randomized in the trial had completed the tool at baseline. Similarly, only 27 of the patients completed the tool at the time of the first clinical assessment. The stated reasons for not completing the tool were that the authors did not think it was appropriate to ask patients to do a QoL survey after they had been told on the same day that there was disease progression. Just as there were no differences in the clinical efficacy between the groups, there was also no difference between the groups in QoL scores. Nevertheless, similar trends were noted in the scores, that is, functional scores remained stable, but there was a worsening on the symptom scores.

The last trial to use the EORTC QLQ-C30 was that of Avril and colleagues [16] who compared dacarbazine with fotemustine. In that study, the tool was given to the patients before randomization, at the end of the induction cycle with the chemotherapeutic agent, at each maintenance infusion and at the end of the study. Of the 229 patients randomized into the trial, only 156 were assessable at the end of the induction period. A larger proportion of those patients not completing the tool had progressive disease or worse performance status, which could have underestimated the impact on QoL that the progressive disease and treatment had on these patients. No differences were noted of those patients that completed the QoL tool, just as there were no differences noted clinically. No analysis was performed beyond the induction phase because of the high drop out rate noted (only 76 patients entered the maintenance phase of the trial).

That trial also appears to be somewhat biased in its reporting of results. In the conclusion of their abstract, they pointed out the statistical significance of fotemustine over dacarbazine with respect to overall response and claimed a "trend" in favor of overall survival. Nevertheless, the significance of the difference between rates of Grades 3 and 4 adverse events that occurred (51% neutropenia and 43% thrombocytopenia with fotemustine, as opposed to 5% and 6%, respectively, with dacarbazine) was not accompanied by a P-value in the Results (abstract or main text) and the difference was not mentioned in the Conclusion. These events undoubtedly would eventually affect QoL.

In a randomized controlled trial of dacarbazine with or without interferon [20], Coates and coworkers found no difference between the treatment groups with respect to survival duration, time to progression and tumor response rate, which was reported in another article [30]. Patients had their QoL assessed using the self-administered GLQ-8 and six other linear analog scales (i.e., physical well-being, mood, pain, nausea and vomiting, appetite, and overall QoL), in addition to a QoL questionnaire completed by the treating physician. In univariate analyses, each individual QoL scale was predictive of subsequent survival, however, when the results were controlled for liver metastases and performance status on multilogistic regression analysis, only the global assessment of QoL (both patient and physician QoL questionnaire) and appetite were statistically significant in predicting survival. The authors were quick to point out that the study did not distinguish between a causative and a trivial relationship between QoL and survival duration, however, they concluded that in future studies of MM that it may be prudent to balance groups based on the patient's QoL. Those authors did not examine the impact of the drugs on QoL.

The last trial by Beusterien and associates [17] used the Quality of Well Being Self-administered questionnaire (QWB-SA), the Overall State of Health item (OSH), and the General Health Perception Item (GHP) to measure any potential difference in QoL in patients receiving interleukin with or without histamine. The QWB-SA has been used in other oncology trials and is scored from 0 which represents death to 1 which represents optimum functioning without symptoms in a number of different domains over the last 3 days. The OSH allows the patient to select the number from 0 to 100, where 0 is the least desirable health state and 100 being perfect health, which best reflects their state of health. The GHP allows the patient to rate their health from 1 to 5 and it then gets transferred into a scale of 0 to 100 where higher scores reflect a higher QoL. Clinically, a survival benefit was seen for those patients with liver metastases who were receiving the combination of products as compared with interleukin monotherapy. Overall there were no statistical differences between the groups in any of the tools used. Nevertheless, given that there may be a survival advantage for some patients with the combination, it is important to note that QoL did not decrease as measured by these tools.

Despite the lack of convincing evidence for cost-effectiveness overall, some patients in those trials did experience increased benefits from some of these drugs or interventions. It is possible that patients may be willing to pay for them when funding agencies decline to add them to their list of benefits. In some cases, for example, patients may prefer to have more frequent screening to assure that their cancer has not progressed. To those individuals, it may be worth the extra cost in terms of reassurance or knowing their clinical status. Similarly, they may wish to pay to receive a drug that offers increased longevity to have more time with their family, which they value.

An interesting observation made by Tengs [31] was that adjusting for quality in cancer studies did not appreciably affect cost-effectiveness decisions. Thus, life-years and QALYs often appear to be not very different. One possibility is that existing instruments may lack the sensitivity to accurately measure humanistic issues that matter to individuals. If so, a lack of significant differences may be due to measurement, rather than the interventions being studied. That would mean that more sensitive instruments need to be developed and validated to detect more subtle changes that are meaningful to patients and their families.

Based on the information obtained in this review, upon initial diagnosis, patients with MM have a high level of functioning. Unfortunately, these patients progress quickly and have a decline in almost all of the major functional areas assessed by the QoL scales and subsequently an increase in the symptoms of their disease and the adverse effects of the therapies used to treat the illness. To date, QoL in these patients has most often been measured by the EORTC QLQ-C36. This method is considered acceptable because extensive work has been performed on validating it in this illness. Other tools are currently under development, which may prove to be a complement to this tool and be able to monitor small changes in the QoL of these patients. It is important to have the option of tools for this disease because QoL is a vital area to consider then treating MM. Given the poor prognosis of the patients with MM, and the lack of a curative treatment, any new agents used in the palliative treatment of this disease should have their effect on the QoL of the patient as all efforts should be made to improve the symptoms of these patients. Also when assessing the QoL, ideally the patient should be asked, however, if asking the patient is not an option, a close relative should be used and unless the tool is validated for this purpose, the opinion of the health-care provider on the QoL of the patient may not be the best measure.

Conclusions

The relative lack of information concerning pharmacoeconomics (i.e., two studies) in the literature identified in our review is not surprising. Because of the poor prognosis of patients with MM, and the lack of a proven treatment, the utility of pharmacoeconomic analyses comparing the different regimens may be questionable, unless there is an advantage due to decreased side effects. Usually, if no treatment can be determined to be better than the other, then a cost minimization strategy is considered best. We agree to statements made in a recent review [4], that what is needed is to identify a "gold standard" of therapy that is consistently better than placebo. In addition to establishing the efficacy of such an agent, it would be ideal if a pharmacoeconomic analysis was conducted along with it to determine whether such a strategy would in fact be cost-effective. Given the assumption that it is unlikely for a placebo controlled trial to be performed, experts suggest that dacarbazine be considered the standard therapy, hence any economic analysis being performed should use this drug as a minimum for its comparison as well [4].

Quality scores from the pharmacoeconomic (i.e., studies comparing both costs and consequences) studies were generally very good and >80%. In contrast, other quality assessments of economic publications from all over the world [9,32,33] have found much lower quality scores than those in this review.

Overall, a definite need exists in this area to determine what the actual current costs are for treating patients with MM are from a societal perspective so that any new therapies can be judged against those as a standard. Additionally, although pharmacoeconomic data may be available for the United States, future work needs to be performed in other countries to ensure that the therapy used is cost-effective in a global environment.

As an effective treatment option is not available for MM at present, future pharmacoeconomic analyses should consider the cost per QALY gained will be and not just the cost for additional life-years gained. Although not covered in this review, another important area for future study will also be on the prevention of MM and thus avoiding the high costs of treatment seen with the treatment of these patients.

It should be noted that, as with the pharmacoeconomic analyses, the success with these drugs has been less than disappointing. The three trials of interferons [20,23,28] failed to find a clinical advantage in favor of that drug. Similarly, temozolomide was found to provide no advantage over the long-time standard, dacarbazine [22] and fotemustine had a marginal impact on only one of several clinical outcomes (i.e., response) [16]. At the same time, none of these clinical trials reported any benefit in terms of QoL. Therefore,

newer drugs with clinical efficacy and which improve patients' QoL are needed.

Quality-of-life data should also influence future trials of MM as it should be considered when randomizing patients into different arms of the trial as it may affect the patient's outcome in the trial. In addition, specific trials examining interventions aimed at improving the QoL of patients may also be performed to determine their impact on the patients' survival with MM. Most importantly though, the QoL portion of future trials must be better performed, ensuring that all patients receiving the experimental therapy complete the QoL portion as well. The trial data on QoL at present have a high dropout rate limiting the value of any conclusions that can be drawn from them.

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