Bortezomib and thalidomide for the first-line treatment of multiple myeloma

The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Multiple myeloma (MM) is the second most common haematological cancer in the UK, characterised by unregulated plasma cell proliferation. In England and Wales there are approximately 3600 new diagnoses recorded annually, and in 2007 most diagnoses were recorded in people aged 75–79 years. Symptoms and clinical features of MM include fatigue, bone pain and/or fracture, anaemia, the presence of M-protein in serum and/or urine, and hypercalcaemia. The aetiology of MM is unknown and malignant cells display a variety of cytogenetic abnormalities. Myeloma is not curable, but can be treated with a combination of supportive measures and chemotherapy. The aim is to extend the duration and quality of survival by alleviating symptoms and achieving disease control while minimising the adverse effects of the treatment. Survival of patients from diagnosis can vary from months to over a decade. Factors affecting prognosis include burden of disease, type of cytogenetic abnormality present, patient-related factors – such as age and performance status – and treatment response factors.

In England and Wales, the choice of first-line treatment depends on a combination of factors. The majority of patients are not able to withstand intensive treatment, such as high-dose chemotherapy with autologous stem cell transplantation (SCT), because of age, specific problems or poor performance status. These patients are therefore offered single-agent or combination chemotherapy (which is less intensive). Typically, combination therapies include chemotherapy with an alkylating agent (such as melphalan or cyclophosphamide) and a corticosteroid (such as prednisolone or dexamethasone). More recent treatment options may also include combination therapies that incorporate drugs such as thalidomide (Thalidomide Celgene®, Celgene, Uxbridge, UK) and bortezomib (Velcade®, Janssen–Cilag, High Wycombe, UK).

Objectives

To assess the clinical effectiveness and cost-effectiveness of bortezomib or thalidomide in combination chemotherapy regimens with an alkylating agent and a corticosteroid for the first-line treatment of MM.

Methods

Data sources

Electronic bibliographic databases, including MEDLINE, EMBASE and The Cochrane Library, were searched from 1999 to 2009 for English-language articles. Bibliographies of articles, grey literature sources and manufacturers' submissions (MSs) were also searched. Experts in the field were asked to identify additional published and unpublished references.

Study selection

Titles and, where available, abstracts were screened for eligibility by two reviewers independently. The inclusion criteria specified in the protocol were applied to the full text of retrieved papers by one reviewer and checked independently by a second reviewer. The inclusion criteria were as follows:

- *Interventions* Bortezomib in combination with an alkylating agent and a corticosteroid for first-line treatment of MM. Thalidomide in combination with an alkylating agent and a corticosteroid for first-line treatment of MM.

- *Comparators* (i) The interventions compared with each other or (ii) melphalan or cyclophosphamide in combination with prednisolone/prednisone or dexamethasone.

- *Population* People with previously untreated MM who are not candidates for high-dose chemotherapy with SCT.

- *Outcomes* Studies had to report one or more of the following outcomes – overall survival (OS); progression-free survival (PFS); time to progression (TTP); response rates; health-related quality of life (HRQoL); cost-effectiveness [such as incremental cost per quality-adjusted life-year (QALY) gained].

The study types that were eligible for inclusion in the systematic review of clinical effectiveness were:

- randomised controlled trials (RCTs); good-quality observational studies could be considered if the data from available RCTs were incomplete.

And for the systematic review of cost-effectiveness, eligible study types were:

- full cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved through discussion at each stage.

Data synthesis

Studies were synthesised through a narrative review with full tabulation of the results of all included studies.

Economic modelling

A cost–utility decision-analytic model was used to compare the cost-effectiveness estimates of bortezomib in combination with melphalan and prednisolone/prednisone (VMP), thalidomide in combination with cyclophosphamide and attenuated dexamethasone (CTDa), and thalidomide in combination with melphalan and prednisolone/prednisone (MPT) versus melphalan and prednisolone/prednisone (MP). The model used a survival analysis approach to estimate the OS and PFS for each of the interventions for a patient with newly diagnosed MM. The model consisted of cycles of 6 weeks in length, to be consistent with the cycle lengths used for chemotherapy treatment. The model survival curves were derived using trial data for the duration of trial follow-up and an exponential distribution was used to extrapolate beyond the length of the trial. Second-line treatment costs were included. The perspective of the analysis was that of the NHS and Personal Social Services (PSS). The model estimated the lifetime costs and benefits of treatment with discount rates of 3.5%. The intervention effect in terms of improvement in OS and PFS was derived from the systematic review of effectiveness. The outcome of the economic evaluation is reported as cost per QALY gained.

Results

Number and quality of studies

A total of 1436 records were screened and 40 references were retrieved for consideration for the systematic review of clinical effectiveness. Five RCTs met the inclusion criteria for the clinical effectiveness systematic review. One RCT evaluated VMP, three evaluated MPT, and one evaluated CTDa. The comparator in all the included trials was MP. Study quality was uncertain for most RCTs because details needed to judge study quality were incompletely reported. All studies stated that the analyses followed intention-to-treat (ITT) principles but none adequately reported the amount and pattern of data censoring. Two RCTs, one of the MPT versus MP trials and the CTDa versus MP trial, had a maintenance phase with thalidomide that did not meet the inclusion criteria. This meant that some results from these trials were not eligible for inclusion in the systematic review.

Summary of benefits and risks

The evidence from one RCT indicated that combination chemotherapy with VMP was more effective than MP in terms of the primary outcome TTP, and the secondary outcomes of OS and the proportion of participants achieving complete response (CR), or achieving a partial response (PR) or better (response outcomes, not ITT). Adverse events (AEs) occurred in both trial arms. The use of bortezomib was associated with a statistically significant increase in grade 3 AEs.

Evidence from two RCTs indicated that MPT was more effective than MP in terms of these trials' primary outcome of OS, and the secondary outcome of PFS. Three trials provided evidence indicating a statistically significant greater proportion of participants receiving MPT achieved CR. (AiC/CiC information has been removed.) AEs occurred in all MPT, CTDa and MP trial arms. The AEs associated with the use of thalidomide were difficult to summarise. The AE that was most consistently, and statistically significantly, associated with the use of thalidomide was peripheral neuropathy. AEs of thrombosis or embolism, somnolence, infections and constipation were reported as being statistically significantly increased in the thalidomide-containing arms of some trials but not others.

Limited evidence on HRQoL was provided by the single trial of VMP versus MP. This indicated that, after the onset of best response, participants treated with VMP had a higher sustained HRQoL improvement rate in 14 of the 15 European Organisation for Research and Treatment of Cancer QoL questionnaire C30 (EORTC QLQ-C30) scores than those participants receiving therapy with MP.

Summary of cost-effectiveness

The systematic review of published economic evaluations identified five abstracts that did not contain enough information for critical appraisal. The systematic review of quality-of-life (QoL) studies did not find any generic preference-based QoL studies that assessed QoL in the population of interest. However, two studies that used the EORTC QLQ-C30 questionnaire were identified and a mapping algorithm was available to map the EORTC QLQ-C30 to the European Quality of Life-5 Dimensions (EQ-5D).

Two manufacturers submitted evidence to be considered for this review:

- Janssen–Cilag, the manufacturer of bortezomib, constructed a survival model that estimated OS and PFS based on treatment effects from a mixed-treatment comparison (MTC) of the trials. They included second- and third-line treatment. The base-case results from the submission found all treatments to be cost-effective. The incremental cost-effectiveness ratio

(ICER) for VMP versus MP is estimated to be £10,498. Furthermore, the ICERs of VMP versus MPT and VMP versus CTDa were estimated to be £11,907 and £10,411, respectively.

- Celgene, the manufacturer of thalidomide, constructed a Markov model with health states for preprogression (with or without AEs), post progression and death. They assumed that survival after disease progression was the same irrespective of first-line treatment. Treatment effects for disease progression were calculated using a random effects MTC. The base-case results from the submission estimated an ICER of £23,381 per QALY gained for MPT versus MP and £303,845 per QALY for VMP versus MPT.

The Southampton Health Technology Assessments Centre (SHTAC) developed an independent survival model. From this independent model, the incremental cost-effectiveness figures versus MP for MPT, VMP and CTDa were £9135, £29,820 and £33,031 per QALY gained, respectively. However, MPT dominated VMP as it was cheaper and more effective.

Sensitivity analyses

The effect of a range of parameter values in the economic model were evaluated in deterministic and probabilistic sensitivity analyses (PSAs). The model results were robust to changes in the parameter values tested. The model results were most sensitive to changes in the values of the hazard ratios for OS. The PSA estimated the probability of each of the treatments to be cost-effective at the £20,000 and £30,000 willingness-to-pay thresholds. MPT has the highest probability of being cost-effective, with probabilities of 0.95 at both the thresholds tested.

Discussion

A systematic review and economic evaluation have been carried out independent of any vested interest but both are associated with some limitations. Only one RCT contributed data on VMP and the published peer-reviewed follow-up data are immature. For MPT, OS data from two trials were eligible for inclusion but the doses of thalidomide differed between the trials and the treatment period was not reflective of current UK practice so the generalisability of the findings is uncertain. No evidence on OS or PFS following treatment with CTDa met the inclusion criteria for the systematic review because of the use of thalidomide maintenance therapy for some participants in the single RCT that assessed this intervention.

No head-to-head trials were identified which compared bortezomib in combination with an alkylating agent and a corticosteroid with thalidomide in combination with an alkylating agent and a corticosteroid.

Assessment of the impact of treatment on quality of life was very limited. Data on HRQoL could be included from only one RCT – the study of VMP versus MP. The single RCT that assessed CTDa versus MP reported HRQoL outcomes but these did not meet the inclusion criteria of the systematic review.

An MTC was not carried out because of doubts about the validity of doing so due to potential differences in participant characteristics, delivery of MP treatment in the comparator arms, and differences in length of follow-up. Furthermore, CTDa could not have been included in such an analysis because the single trial that assessed CTDa included randomisation to maintenance therapy for some participants.

The review of clinical effectiveness has found that VMP and MPT can both be considered more clinically effective than MP for the first-line treatment of MM in people for whom high-dose

therapy and SCT would not be appropriate. CTDa is more effective than MP in terms of CR but data on survival outcomes did not meet the inclusion criteria of the clinical effectiveness systematic review.

The review of QoL found that the only HRQoL studies for the population of interest had used a disease-specific HRQoL measure. Therefore, EQ-5D utility estimates used in the SHTAC model had to be derived using a mapping algorithm. The OS outcome from the single trial of CTDa versus MP did not meet the inclusion criteria for the systematic review of clinical effectiveness (as some patients in this trial received thalidomide maintenance therapy) but CTDa was included in the cost-effectiveness analysis because it is a relevant comparator. (AiC/CiC information has been removed.)

The results from the cost-effectiveness analyses submitted by the two manufacturers and the results from the SHTAC cost-effectiveness model varied considerably. These variations arise because of differences in the modelling approaches taken and the data used to populate each model. Costs vary substantially between the analyses. Key contributors to the variation in costs were differences in costs included for subsequent treatments, and differences in assumptions made about the mean number of vials of bortezomib used. Incremental QALY estimates for MPT versus MP also varied widely.

Cost-effectiveness analysis indicates that MPT has a greater probability of being cost-effective than either VMP or CTDa. Results for CTDa, however, should be treated with caution because this trial included maintenance therapy with thalidomide for some patients. (AiC/CiC information has been removed.)

Conclusions

Service provision is unlikely to change greatly; however, uncertainties remain and further research is needed. In particular, head-to-head trials of bortezomib- and thalidomide-containing combination regimens are desirable. These trials should include assessments of patient HRQoL in response to treatment. It is not known whether the choice of second-line treatment or the sequence of treatments affects patient outcomes.

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