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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CRD summary
This review concluded that bortezomib or thalidomide in combination with melphalan and prednisolone/prednisone could be considered more effective than melphalan and prednisolone/prednisone for the first-line treatment of multiple myeloma. Further head-to-head trials of bortezomib- and thalidomide-containing combination regimens were required. These conclusions reflect limitations in the evidence base and are likely to be reliable.

Authors' objectives
To assess the clinical effectiveness of bortezomib or thalidomide in combination chemotherapy regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma.

This abstract only addressed part of the report related to clinical effectiveness.

Searching
The following databases were searched from 1999 to 2009 for English language studies: MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, DARE, HTA, Cochrane Central Register of Controlled Trials (CENTRAL) and Web Of Science. The search strategy was presented. Grey literature sources and the manufacturers' submissions were searched. Reference lists of relevant publications were screened and experts in the field were contacted for any additional relevant studies.

Study selection
Randomised controlled trials (RCTs) and good-quality observational studies that evaluated bortezomib in combination with an alkylating agent and a corticosteroid, or thalidomide in combination with an alkylating agent and a corticosteroid were eligible for inclusion. Participants had to be patients with previously untreated multiple myeloma who were not candidates for high-dose chemotherapy with stem cell transplantation. The eligible comparators were melphalan or cyclophosphamide in combination with prednisolone/prednisone or dexamethasone, as well as targeted interventions that compared each other. Relevant conference proceedings were eligible for inclusion only if sufficient details were presented to allow quality assessment. The eligible studies had to report at least one of the following outcomes: overall survival; progression-free survival; time to progression; response rates; health related quality of life (HRQoL). Adverse events of treatment were reported when available within the trials that met the inclusion criteria.

Most included studies evaluated thalidomide in combination with melphalan and prednisolone/prednisone. The comparator in all included studies was melphalan and prednisolone/prednisone. The patients' age ranged from 18 to 75 years, where reported. All included studies were multicentre RCTs, with a median follow-up that ranged from 16.3 to 51.5 months, where reported.

Two reviewers independently assessed studies for inclusion, with discrepancies resolved by a third reviewer.

Assessment of study quality
The quality of studies was assessed using the following criteria: randomisation, allocation concealment, baseline comparability, blinding, drop-out imbalance, more outcomes than reported, intention-to-treat analysis and missing data accounted for.

Quality assessment was performed by one reviewer and checked by a second reviewer, with any disagreements resolved by a third reviewer.

Data extraction
Data were extracted on event rates to enable the calculation of risk ratios (RRs) or hazard ratios (HRs) with 95%
confidence intervals (CIs). Where standard errors (SEs) of log-HRs were not reported, standard errors were estimated using the method by Tierney and colleagues.

Data extraction was performed by one reviewer and checked by a second reviewer, with any disagreements resolved by a third reviewer.

**Methods of synthesis**
The studies were combined in a meta-analysis where appropriate. The pooled risk ratios or hazard ratios, with 95% confidence intervals, were calculated using a fixed-effect model. Statistical heterogeneity was assessed using the X² and I² statistics.

**Results of the review**
Five RCTs were included in the review (1,566 patients including four trials, where reported). All trials used intention-to-treat analysis but none adequately reported the amount and pattern of data censoring. Randomisation was adequate in two trials, and allocation concealment was adequate in three trials. Baseline comparability was adequate in four trials, but blinding was not adequate in most trials.

**Bortezomib in combination with melphalan and prednisone (one RCT):** One RCT reported that compared with melphalan and prednisolone/prednisone, bortezomib in combination with melphalan and prednisone was more effective in terms of overall survival, time to progression and the proportion of participants who achieved a complete response or achieving a partial response.

**Thalidomide in combination with melphalan and prednisone (three RCTs):** Compared with melphalan and prednisolone/prednisone, thalidomide in combination with melphalan and prednisolone/prednisone was more effective in terms of overall survival (two RCTs) and progression-free survival (two RCTs). Thalidomide in combination with melphalan and prednisolone/prednisone was also associated with a significant increase in the proportion of participants achieving complete response (three RCTs). No significant heterogeneity was observed for these outcomes.

**Thalidomide in combination with cyclophosphamide and attenuated dexamethasone (one RCT):** One RCT reported that compared with melphalan and prednisolone/prednisone, thalidomide in combination with cyclophosphamide and attenuated dexamethasone was more effective in terms of complete response. Data on survival outcomes did not meet the inclusion criteria.

In terms of adverse events, one RCT reported that bortezomib therapy was associated with a significant increase in grade 3 (severe) adverse events. The most commonly reported adverse event associated with the use of thalidomide was peripheral neuropathy. A range of adverse events (including thrombosis, embolism, somnolence, infections and constipation) were reported as being significantly increased in the thalidomide-containing arms of some trials.

Results for other outcomes were also reported.

**Authors’ conclusions**
Bortezomib or thalidomide in combination with melphalan and prednisolone/prednisone could be considered more clinically effective than melphalan and prednisolone/prednisone for the first-line treatment of multiple myeloma patients for whom high-dose therapy and stem cell transplantation would not be appropriate. Further head-to-head trials of combination chemotherapy regimens that contained bortezomib versus regimens containing thalidomide were required.

**CRD commentary**
This review’s inclusion criteria were clear. Several relevant databases were searched. Efforts were made to find both published and unpublished studies, which reduced the potential for publication bias. Only studies in English language were included, which may have increased the risk of language bias. Sufficient attempts were made to minimise the errors and biases in the review process. Appropriate criteria were used to assess study quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results where appropriate. This review was generally well conducted. The authors’ conclusions reflected limitations in the evidence base and recommendations for future research were appropriate. These conclusions are likely to be reliable.
Implications of the review for practice and research

**Practice:** The authors stated that, although there would be additional intravenous administration to cover if the use of bortezomib was extended, service provision was unlikely to change considerably.

**Research:** The authors stated that further head-to-head trials of combination chemotherapy regimens that contained bortezomib versus regimens that contained thalidomide were required. These trials should include an evaluation of patient HRQoL in response to treatment. If the studies were conducted to assess the impact of second-line treatments on patient outcomes, they should assess whether the sequence of treatment (such as first-line therapy with a thalidomide-containing regimen followed by second-line treatment with a bortezomib-containing regimen; or vice versa) had any impact on patient outcomes.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.