Thalidomide maintenance therapy for patients with multiple myeloma: meta-analysis

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CRD summary
The authors concluded that thalidomide maintenance therapy in combination with steroids was effective in prolonging survival in multiple myeloma. Intolerance and adverse effects (venous thrombosis, peripheral neuropathy) were frequent. The authors' conclusions reflect the evidence presented but there were limitations in the review methodology and study quality was unclear so the reliability of the evidence is unclear.

Authors' objectives
To evaluate the effects of thalidomide maintenance therapy on overall survival in previously untreated or relapsed patients with multiple myeloma.

Searching
PubMed (up to October 2011), The Cochrane Library, Current Controlled Trials and ClinicalTrials.gov were searched as well as relevant haematology and oncology conference proceedings (up to 2010). Search terms were briefly indicated. Reference lists of included studies and relevant systematic reviews and guidelines were searched for additional studies. There were no language or publication restrictions.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared thalidomide-containing maintenance regimens with observation or non-thalidomide-containing maintenance regimens. Participants were patients with newly diagnosed multiple myeloma treated with standard chemotherapy or induction chemotherapy followed by high dose chemotherapy and autologous stem cell transplantation. Studies that used bortezomib in combination with thalidomide were excluded. Trials had to have a follow-up period of at least two years since maintenance therapy. The primary outcome was overall survival. Secondary outcomes were progression-free survival (defined as time from the date of randomisation to the time of first progression or death from any cause), disease status (European Group for Blood and Marrow Transplantation criteria, very good partial response) and treatment-related adverse events (venous thrombosis and peripheral neuropathy; National Cancer Institute Common Toxicity Criteria grade 3 or higher events).

Median age of patients ranged from 57 to 73 years. At the beginning of maintenance therapy between 34% and 55% of patients had less than a very good partial response (where reported). In most trials, patients were randomised at the beginning of maintenance therapy. Thalidomide was administered alone or in combination with corticosteroids or interferon. Routine prophylaxis for venous thrombosis was used rarely. Median duration of thalidomide treatment (where reported) ranged between seven and 30 months.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Quality assessment was carried out by one reviewer and checked by a second reviewer. Any discrepancies were resolved by consensus. The authors did not provide any detail of criteria used for quality assessment or any summary of the quality assessment carried out.

Data extraction
Data extraction was carried out by one reviewer and checked by a second reviewer. Any discrepancies were resolved by consensus. Survival data were expressed as hazard ratios with 95% confidence intervals and adverse events data as risk difference.

Methods of synthesis
Meta-analysis was carried out using a DerSimonian and Laird random-effects model with inverse variance weighting. Heterogeneity was assessed using $\chi^2$ and $I^2$ and explored in subgroup analyses (cointervention with steroids, different induction therapies, response status).
Sensitivity analyses were carried out to assess the extent to which any one study influenced the overall results of the meta-analysis.

Results of the review
Six trials were included in the review (2,786 patients, range 64 to 345 per comparison group). Study quality was not reported. Between 13% and 52% of patients stopped thalidomide treatment because of intolerance (reported in four trials).

Taking all studies together there was no significant improvement in overall survival with thalidomide maintenance therapy (hazard ratio 0.83, 95% CI 0.67 to 1.02; p=0.07; significant heterogeneity I²=50.6%). In the three trials that used concomitant therapy with steroids there was a significant benefit for overall survival (hazard ratio 0.70, 95% CI 0.52 to 0.94; p<0.05). The three trials that did not use steroid therapy demonstrated no significant benefit for overall survival (hazard ratio 1.00, 95% CI 0.83 to 1.20). When analysing the data according to differences in induction therapy, there was no clear effect.

Thalidomide maintenance therapy showed a significant benefit for progression-free survival (hazard ratio 0.65, 95% CI 0.59 to 0.73; p<0.01; six studies; no significant heterogeneity I²=14%) and irrespective of concomitant steroid therapy.

In the treatment groups there was a significantly increased risk of venous thrombosis (risk difference 0.024, 95% CI 0.004 to 0.045; p=0.02; five studies) and peripheral neuropathy (risk difference 0.072, 95% CI 0.049 to 0.095; p<0.01; four studies; no significant heterogeneity).

Authors’ conclusions
The results suggested that thalidomide maintenance therapy in combination with steroids was effective in prolonging survival in multiple myeloma. Adverse effects included increased rates of venous thrombosis and peripheral neuropathy.

CRD commentary
The review question and inclusion criteria were clear. There was a comprehensive literature search of relevant sources. There were no restrictions on language, publication date or publication status. It was unclear whether study selection was carried out with sufficient attempts to minimise error and bias. Data extraction was checked in order to minimise bias. Quality assessment was mentioned but no criteria were given and no quality summary of included studies was provided so that it was unclear how reliable the included studies were. Study details were provided adequately. Suitable methods were used for meta-analysis and assessment of heterogeneity.

The authors’ conclusions reflect the evidence presented but because of the lack of quality assessment it was unclear how robust the evidence was. It should also be noted that a substantial proportion of patients had to stop thalidomide treatment because of intolerability.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that more research was needed on any synergistic effects between thalidomide and steroids and on lenalidomide (a thalidomide analogue with less frequent side effects). More studies were required on patients who were ineligible for autologous stem cell transplantation, on myeloma subtypes and on disease status of patients at the start of maintenance therapy to enable optimal selection of patients for maintenance therapy. Effects of use of thalidomide during induction chemotherapy should be investigated.

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