A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma

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CRD summary
This review assessed the efficacy and toxicity of thalidomide medications for adult patients with previously untreated multiple myeloma. The authors concluded that thalidomide medication improves patients' overall survival. However, it is also associated with an increased risk of venous thromboembolism (VTE). The review was generally well-conducted and the conclusion is likely to be reliable.

Authors' objectives
To assess the efficacy and toxicity of thalidomide for adult patients with previously untreated multiple myeloma.

Searching
The following databases were searched without language restriction from inception to November 2007: MEDLINE, EMBASE, and the Cochrane Library. The search terms were reported. Conference proceedings from the American Society of Hematology and the American Society of Clinical Oncology were searched from 1999. The reference lists of relevant publications were also screened.

Study selection
Randomised controlled trials (RCTs) which compared thalidomide at any dose, for any duration, as monotherapy or in combination with corticosteroid or chemotherapy, with controls in adult patients with previously untreated myeloma of any stage were eligible for inclusion. Only studies in which the controls were melphalan plus prednisone, dexamethasone monotherapy, and dexamethasone combined with anthracycline-based chemotherapy were eligible for inclusion. The primary review outcome was overall survival. Secondary outcomes were progression outcomes, overall response rate, complete response rate and adverse event rates.

Included RCTs investigated induction thalidomide in the absence or presence of autologous stem cell transplantation (ASCT), and some evaluated maintenance thalidomide after ASCT. All except two studies allowed the use of combination therapy with a range of concomitant treatments.

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

Assessment of study quality
The quality of studies was assessed using the following criteria: final analysis reported; concealment of randomisation; masking of intervention; blinded outcome assessment; completeness of follow-up; and intention-to-treat analyses.

Two reviewers independently performed the validity assessment, but the authors did not state how the disagreements were resolved.

Data extraction
It appears that the authors extracted data on the point estimates for overall survival, response rate, adverse event, hazard ratio (HR) and relative risk (RR). Hazard ratios and relative risks, with 95% confidence interval, were estimated if not available from trial reports. It appears that the authors used intention-to-treat data in analyses where possible. Study authors were contacted for missing data.

Two reviewers independently extracted the data from studies, with any disagreements resolved by a third reviewer.

Methods of synthesis
The studies were combined in meta-analyses using random-effects models of DerSimonian and Laird. Weighted hazard ratios for overall survival, weighted relative risk of response and adverse events, with 95% confidence intervals (CIs), were calculated. The studies were weighted using the inverse variance method. Statistical heterogeneity was investigated using Cochrane $^2$ and $I^2$ statistics.

Sensitivity analyses were conducted on different response rates reported by published and unpublished studies. Publication bias was not assessed due to the small number of included studies.

**Results of the review**

Thirteen RCTs (n= 4,144) were included in meta-analyses, nine of which reported time-to-event statistics. Seven RCTs were published as full papers and six in abstract form only. Methodological quality varied between trials. Almost all trials reported intention-to-treat analyses. However, only seven trials reported the concealment of randomisation. Masking of intervention and outcome assessment was inadequate in most trials.

When the studies were pooled, for RCTs evaluating induction thalidomide, thalidomide was significantly associated with an improvement of overall survival when added to standard non-transplantation therapy (HR 0.67, 95% confidence interval, CI: 0.56, 0.81, p<0.0001; four RCTs).

For RCTs evaluating maintenance thalidomide following ASCT, thalidomide was not significantly associated with an improvement in overall survival (HR 0.61, 95% CI: 0.37, 1.01, p=0.05; four RCTs). When excluding one trial that evaluated induction and maintenance therapy, thalidomide was significantly associated with a survival advantage (HR 0.49, 95% CI: 0.32, 0.74, p=0.0007; three RCTs).

The addition of thalidomide to standard induction therapy significantly improved myeloma response rate (RR 1.50, 95% CI: 1.33, 1.68, p<0.00001; nine RCTs), and complete response to induction thalidomide (RR 2.82, 95% CI: 1.80, 4.41, p<0.00001; nine RCTs). Induction thalidomide was significantly associated with an increased risk of venous thromboembolism (VTE) (RR 2.56, 95% CI: 1.89, 3.49, p<0.00001; 10 RCTs), as was maintenance thalidomide (RR 1.95, 95% CI: 1.15, 3.30, p<0.01; three RCTs).

Statistically significant heterogeneity was observed in the outcome of overall response rate (p=0.0009, $I^2$ = 69.8%) and complete response rate (p=0.06, $I^2$ = 47.1%). Sensitivity analyses of response rates between published and unpublished studies did not materially affect the results.

**Authors’ conclusions**

Thalidomide medications as induction or maintenance agents were associated with an improvement of overall survival in patients with newly diagnosed multiple myeloma, as well as an increased risk of VTE.

**CRD commentary**

The review inclusion criteria were clear. Several relevant databases were searched. Efforts were made to find both published and unpublished studies, which limits the possibility of publication bias. No language restrictions were applied, which limits the possibility of language bias. Steps were taken to minimise bias by having more than one reviewer independently undertake the study selection, data extraction and validity assessment. Relevant criteria were used to examine the study quality. However, details of the primary studies were limited, for example, the duration of follow-up and patients’ disease stages in each trial were not reported.

Appropriate statistical methods were used to pool the results. Statistical heterogeneity was explored as well as assessed. Although significant heterogeneity was found in the outcome of overall and complete response rate, the studies generally showed the same direction of effects. This review was generally well-conducted. The authors’ conclusions reflect the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors stated that thalidomide, melphalan and prednisone can be the new standard for patients not undergoing ASCT. However, it is more difficult to determine the ideal treatment for patients undergoing ASCT.
Research: The authors stated that studies are required to clarify the overall survival benefit of maintenance thalidomide when it is used both as an induction agent pre-ASCT and as a maintenance agent post-ASCT.

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