Thalidomide and prednisolone versus prednisolone alone as consolidation therapy after autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the ALLG MM6 multicentre, open-label, randomised phase 3 study

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Summary

Background We previously showed that consolidation therapy with thalidomide and prednisolone improved progression-free and overall survival in patients with multiple myeloma who had undergone autologous stem-cell transplantation. We aimed to assess whether these survival advantages were durable at 5 years.

Methods The ALLG MM6 trial was a multicentre, open-label, randomised phase 3 trial done between Jan 13, 2002, and March 15, 2005, at 29 sites in Australia and New Zealand. Patients with newly diagnosed multiple myeloma were randomly assigned (1:1), via computer-generated randomisation charts, to receive indefinite prednisolone maintenance alone (control group) or in combination with 12 months of thalidomide consolidation (thalidomide group) after autologous stem-cell transplantation. Randomisation was stratified by treating centre and pre-transplantation concentrations of β_2 microglobulin. Patients and treating physicians were not masked to treatment allocation. Primary endpoints were progression-free survival and overall survival. Analysis was by intention to treat. Secondary endpoints were overall response to salvage therapy, incidence of second primary malignancy incidence, and cost-effectiveness. This trial is registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12607000382471.

Findings We randomly assigned 269 patients to the thalidomide (n=114) or control group (n=129). After a median follow-up of 5·4 years (IQR 3·1–7·2), estimated 5-year progression-free survival was 27% (95% CI 23–32) in the thalidomide group and 15% (11–18) in the control group (hazard ratio [HR] 0·16, 95% CI 0·044–0·58; p=0·0054) and 5-year overall survival was 66% (95% CI 61–70) and 47% (42–51), respectively (HR 0·12, 95% CI 0·028–0·56; p=0·0072). There was no difference in overall response to salvage therapy, survival post-progression, or incidence of secondary malignancies between the two groups. Incremental cost-effectiveness ratio was AUS$26 996 per mean life-year gained.

Interpretation Consolidation therapy with thalidomide and prednisolone after autologous stem-cell transplantaion is an acceptable therapeutic approach when alternative drugs are not available.

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Introduction

Since the introduction of novel drugs, the survival of patients with multiple myeloma has continued to improve,[1,2] and for eligible patients, high-dose melphalan followed by autologous stem-cell transplantation is the standard of care. However, multiple myeloma is essentially an incurable disease, with almost all patients relapsing. Consolidation and maintenance strategies using novel drugs to improve survival after autologous stem-cell transplantation continue to be explored.

We previously reported the clinical outcomes of patients enrolled in the Australasian Leukaemia and Lymphoma Group (ALLG) MM6 trial.[3,4] This trial was designed to assess the effect of a fixed duration of low-dose thalidomide and prednisolone when used as consolidation therapy after high-dose melphalan-conditioned autologous stem-cell transplantation for the initial management of patients with multiple myeloma compared with prednisolone alone. At a median follow-up of 3 years after randomisation, addition of a maximum of 12 months of thalidomide prolonged both overall survival and progression-free survival compared with prednisolone alone (3-year progression-free survival: 42% *vs* 23%; p<0·001 and 3-year overall survival: 86% *vs* 75%; p=0·004). Furthermore, thalidomide consolidation did not adversely affect post-relapse survival in the subsequent salvage setting.

Here we describe the results of the final analysis of the ALLG MM6. We assessed whether the survival advantage for thalidomide and prednisolone consolidation after autologous stem-cell transplantation was durable. Moreover, in view of the ever increasing financial burden associated with cancer-related health-care costs, we sought to retrospectively assess the cost-effectiveness of the intervention.

Methods

Study design and patients

The ALLG MM6 trial was a multicentre, open-label, randomised phase 3 trial done between Jan 13, 2002, and March 15, 2005, at 29 sites in Australia and New Zealand. Details of the participating sites are listed in the appendix. The study protocol and clinical results have been described previously.[3] Patients aged 26–74 years with symptomatic multiple myeloma who were planning to have autologous stem-cell transplantation were registered within 4 weeks of undergoing the procedure. Previous induction therapy was at the discretion of the attending physician. We included patients who did not have evidence of progressive disease 42–50 days after transplantation, those who had haemopoietic reconstitution, and those with a European Cooperative Oncology Group (ECOG) performance status score of less than 3.

See Online for appendix

The protocol was approved by the relevant institutional ethics review boards and all patients provided written informed consent in accordance with the Declaration of Helsinki.

Randomisation and masking

Patients were randomly assigned (1:1), via computer-generated randomisation charts, to receive alternate-day oral prednisolone and indefinite monthly intravenous zoledronic acid (4 mg) either with (thalidomide group) or without (control group) oral thalidomide. Randomisation was stratified by treating centre and pre-transplantation concentrations of β_2 microglobulin (<4 mg/L *vs* ≥4mg/L). Patients and treating physicians were not masked to treatment allocation.

Procedures

Patients assigned to thalidomide received 100 mg daily, increasing to 200 mg daily if tolerated after 14 days, for a maximum of 12 months. Prednisolone (50 mg) was given on alternate days and continued indefinitely or until disease progression. Dose reductions of thalidomide (to a minimum of 100 mg alternate days) and prednisolone (to a minimum of 25 mg on alternate days) were allowed for treatment-related side-effects at the discretion of individual investigators. Patients were assessed every 4 months for disease response according to European Group for Blood and Marrow Transplantation (EBMT) criteria, with inclusion of a category for very good partial response, as defined by the Intergroupe Françoise du Myelome (IFM).[5,6]

For the **Pharmaceutical Benefits Scheme** see http://www.pbs.gov.au

For the **Medicare Benefits Schedule** see http://www9.health.gov.au/mbs/search.cfm

Outcomes

Our primary outcome was progression-free survival and overall survival, with an aim to establish whether significant survival advantages evident with thalidomide and prednisolone at a median follow-up of 3 years were durable at 5 years. We measured progression-free survival from the date of maintenance randomisation to the the date of relapse, progression, or death from any cause, whichever occurred first. Patients who had not relapsed, progressed, or died by the study close-out date (Dec 31, 2012) had their progression-free survival censored at that date unless they were lost to follow-up, in which case they were censored at the date they were last known to be alive. We measured overall survival from the date of maintenance randomisation. We censored patients who had not died by the study close-out date. For secondary outcomes we compared the proportion of patients with an overall response to salvage therapy, and assessed the incidence of second primary malignancy and the cost-effectiveness of thalidomide after autologous stem-cell transplantation. We defined an overall response as partial response, very good partial response, or complete response, as per International Myeloma Working Group uniform response criteria.[7] We measured post-relapse survival from the date of confirmed disease progression. We did not obtain data for long-term adverse events, other than that for second primary malignancy.

Statistical analysis

We anticipated that for the analysis of overall survival a minimum of 135 events would take place, providing greater than 80% power to show hazard ratios (HRs) less than 0·60 as being statistically significant (two tailed α=0·05). We compared progression-free survival and overall survival between the two study groups with Cox's proportional hazards models adjusted for initial response to autologous stem-cell transplantation (more than or equal to a very good partial response *vs* less than a very good partial response) and pre-transplantation concentrations of β_2 microglobulin (≥4 mg/L *vs* <4 mg/L). We assessed the assumption of consistent proportional hazards for each factor in the Cox regression models by testing the significance of the interaction of the log (time) by factor interactions within the Cox regressions. When a categorical covariate in the model violated this assumption, we stratified the regression model on the basis of this factor. We assessed the effects of duration of thalidomide exposure and total cumulative dose on survival with the same Cox's proportional hazards model. Time-to-event data are displayed with Kaplan-Meier curves.

We tested post-relapse survival with the log-rank test from date of progression in each subgroup and categorised response to salvage therapy as thalidomide based, lenalidomide based, bortezomib based, or other (including second autologous stem-cell transplantation and radiotherapy). We compared response to salvage therapy with Fisher's exact tests. Data for time to second primary malignancy were obtained retrospectively, compared between groups with a log-rank test, and summarised as incidence per 100 person-years. Analysis was by intention to treat. We did all analyses with SPSS (version 19.0). This trial is registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12607000382471.

Cost-effectiveness analysis

We did the post-hoc economic analysis as a trial-based analysis without adjustment for baseline factors, duration of exposure, or other variations, and compared the costs and outcomes of the thalidomide group with those of the control group in the post-autologous stem-cell transplantation setting. For the average patient within the two treatment groups, the analysis considered treatment exposure to the primary drug (thalidomide, including interruptions, delays, alternate dosing) and any cotherapies (prednisolone, zoledronic acid), use of ongoing medical and diagnostic services, occurrence of serious adverse events and therapies used to treat those events (largely in-hospital treatment), post-progression therapy, and survival duration. We compared the outcomes across treatment group to derive the incremental cost per life-year gained. We estimated mean life-years (survival) as the area under the Kaplan-Meier curve for each of the two treatment groups, with corresponding standard 95% CIs.

Drug use was as recorded during the course of the trial, with the exception of post-progression therapy. For those therapies, only the name of the treatment was known and use was therefore derived on the basis of published protocols.[8–10] Occurrence of adverse events resulting in treatment was reported for patients in the study. Reports included information about the clinical diagnosis, for which a cost was estimated on the basis of use of Australian Refined Diagnosis-Related Groups (AR-DRG) for events of hospital admission, and costs for pharmaceutical drugs and outpatient medical services, as described in the case report files for adverse events.

Prices are at 2013 levels and all costs are expressed in Australian dollars (AUS$). We sourced drug prices from the Pharmaceutical Benefits Scheme, accessed in May, 2013. We derived prices for medical and diagnostic services used in the analysis from the Medicare Benefits Schedule. We costed all inpatient services (eg, for treatment of serious adverse events) with the cost weight according to the relevant diagnosis-related group (AR-DRG classification, version 6), accessed in May, 2013.

We did sensitivity analyses to test the robustness of the results to variations in assumptions about post-progression therapy and the use of medical services and diagnostic procedures. All costs and outcomes occurring beyond 12 months were discounted at 5% per year (consistent with Australian institutional requirements).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

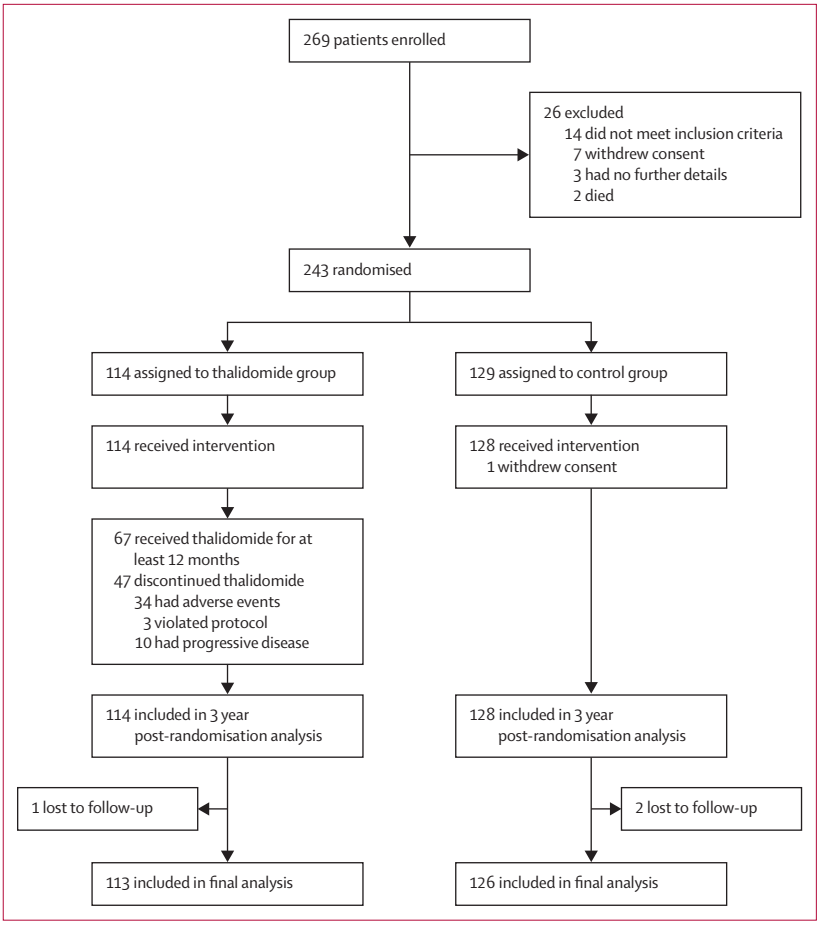

***Figure 1*: Trial profile**

	Thalidomide group (n=114)	Control group (n=129)
Sex		
Male	78 (68%)	102 (79%)
Female	36 (32%)	27 (21%)
Age (years)	57 (26–72)	57 (31–74)
Time from diagnosis to registration (days)	228 (88–1765)	230 (84–3248)
ECOG score		
0	64 (56%)	70 (54%)
1	42 (37%)	56 (43%)
2	2 (2%)	1 (1%)
Unknown	6 (5%)	3 (2%)
β_2-microglobulin concentration (mg/L)		
<4	108 (95%)	114 (88%)
≥4	6 (5%)	15 (12%)
Post-ASCT response		
Complete response or very good partial response	44 (39%)	53 (41%)
No complete response or very good partial response	70 (61%)	76 (59%)

Data are n (%) or median (range), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. ASCT=autologous stem-cell transplantation.

***Table 1*: Patient characteristics at the time of ASCT, and post-ASCT disease response**

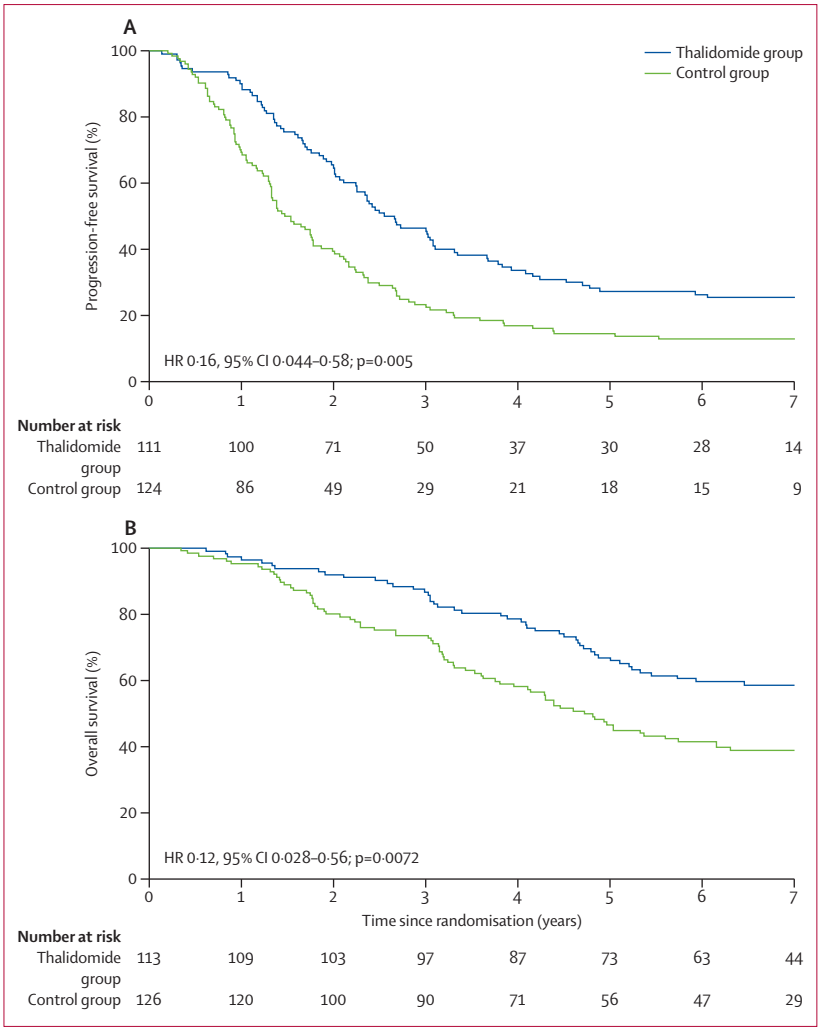

Figure 2: **Kaplan-Meier curves showing progression-free survival (A) and overall survival (B) by treatment group**
HR=hazard ratio.

Results

Figure 1 shows the trial profile. 269 patients were enrolled, and after 26 were excluded, 243 patients were randomly assigned to the thalidomide (n=114) or control group (n=129) 6 weeks after autologous stem-cell transplantation. One patient in the control group withdrew consent following randomisation and was excluded from long-term follow-up. After a median follow-up of 5·4 years (IQR 3·1–7·2) after randomisation, three (1%) of 242 patients were lost to follow-up after the 3 year analysis, leaving 239 patients for final analysis (figure 1). Patient characteristics at the time of autologous stem-cell transplantation were roughly similar between treatment groups (table 1). Induction therapy was well matched between groups and included vincristine, doxorubicin, and dexamethasone (thalidmoide group: n=56; control group: n=63); cyclophosphamide, idarubicin, and dexamethasone (n=23 *vs* n=19); prednisone, cyclophosphamide, doxorubicin, and carmustine (n=13 *vs* n=16); and cyclophosphamide, vincristine, doxorubicin, and methylprednisolone (n=5 *vs* n=10). At the time of trial initiation, the specific prognostic effect of now well described diagnostic karyotypic and FISH-detectable abnormalities in patients with multiple myeloma had not been clarified and such analyses were not routinely available.

Estimated 5-year progression-free survival was 27% (95% CI 23–32) in the thalidomide group and 15% (11–18) in those in the control group (HR 0·16 [95% CI 0·044–0·58], p=0·0054). 5-year overall survival was 66% (95% CI 61–70) the thalidomide group and 47% (42–51) in the control group (0·12 [95% CI 0·028–0·56], p=0·0072; figure 2). Patients in the thalidomide group had a median progression-free survival of 2·7 years (95% CI 2·1–3·2) compared with 1·5 years (1·1–1·8) in the control group. Median overall survival was 8·5 years (95% CI 7·4–9·7) in the thalidomide group compared with 4·5 years (3·9–5·1) in the control group. Events by treatment group are listed in the appendix.

When stratification factors were taken into account, for progression-free survival, thalidomide was beneficial if the pre-autologous stem-cell transplantation concentration of β_2 microglobulin was less than 4 mg/L (p=0·0023; appendix). For overall survival, thalidomide remained significant for pre-transplantation concentrations of β_2 microglobulin of 4 mg/L or more (p=0·0042), but not for concentrations of less than 4 mg/L (p=0·053; appendix). No statistically significant benefit was shown in progression-free (p=0·32) or overall survival (p=0·36) for patients receiving thalidomide who had achieved a very good partial response or better before randomisation (appendix).

In a post-hoc analysis we assessed whether thalidomide and prednisolone for less than 12 months might confer survival benefit. In this assessment, we stratified patients who received thalidomide into those who had at least 4, 8 or 12 months of thalidomide treatment (including those who discontinued because of progression or for other reasons, including toxic effects; figure 3). We compared survival between these groups and with the control group (figure 3). Patients who had 8–12 months of thalidomide had a progression-free survival (p=0·0006) and overall survival (p<0·0001) advantage compared with the control group (figure 3). Furthermore, patients who had 8–12 months of thalidomide had a progression-free and overall survival advantage compared with those who had less than 8 months of treatment (p=0·032 and p=0·013, respectively). There was no difference in progression-free or overall survival for patients who received fewer than 8 months of thalidomide compared with the control group (p=0·651 and p=0·885, respectively; figure 3 and appendix).

Landmark analyses confirmed that survival benefits were gained after a minimum of 8 months of therapy (appendix). Specifically, when patients in the thalidomide group without progressive disease at 8 months after autologous stem-cell transplantation were divided into those who were or were not continuing thalidomide, a clear subsequent progression-free survival advantage

was shown for those who remained on therapy (appendix). Similarly, we noted a significant benefit in overall survival for patients remaining on thalidomide for a minimum of 8 months (appendix).

At the time of assessment, 188 patients (83 [73%] in the thalidomide group and 105 [83%] in the control group) had had disease progression. Of the 96 patients who had available information (42 in the thalidomide group and 54 in the control group) about response to salvage therapy, the overall response rate to salvage therapy was similar irrespective of group (p=0·54; table 2). Furthermore, there was no difference between the groups in post-relapse survival (figure 4), which is consistent with there being no significant difference in overall response rate to salvage therapy between groups for the 188 patients as a whole (data not shown).

There was no difference in incidence of secondary primary malignancy. Of the 207 patients with data available (104 [92%] in the thalidomide group and 103 [82%] in the control group), 19 secondary primary malignancies were reported (ten in the thalidomide group and nine in the control group; log-rank p=0·99), corresponding to an incidence of 1·70 per 100 patient-years in the thalidomide group and 1·67 per 100 patient-years in the control group. Median onset of secondary primary malignancy after randomisation was 51 months (range 11–87) in the thalidomide group and 53 months (11–90) in the control group.

Estimated mean life-years gained were 5·07 years (SD 2·23) for the thalidomide group versus 4·15 years (2·48) for the control group, with a resultant difference of 0·92 years (95% CI 0·31–1·52) discounted. The Pharmaceutical Benefits Scheme publicly funds thalidomide in Australia for all stages of treatment at $1680 per 56×100 mg tablets. In this study the average cumulative dose of thalidomide per patient (n=113) was 46 611 mg, with an average daily dose of 155 mg per day. The difference in drug costs was an additional $21 249 for the average patient in the thalidomide group compared with the control group (table 3). Use of zoledronic acid contributed an additional $1975 to the incremental cost for the thalidomide group and post-progression therapy contributed $5268 (table 3). The estimated difference in the cost of medical and diagnostic services was $2859 (table 3); the key driver of this difference was the infusion cost associated with zoledronic acid, contributing $1652. The average cost per patient for the treatment of a serious adverse event was less than $3000 for the thalidomide group and less than $2000 for the control group (table 3). Outpatient costs contributed $125 (4·7%) to the total cost of treatment for the thalidomide group and $142 (7·6%) to the total cost in the control group. The manner in which outpatient costs were estimated was therefore unlikely to affect the cost of serious adverse events or the resulting cost-effectiveness analysis.

When we combined the difference in treatment costs for drugs, medical services and diagnostics, and serious adverse events, the resulting incremental cost per average patient was $24 912 (discounted) for the thalidomide group versus the control group (table 3). Primary drug therapy was the major contributor to the difference in the average costs per patient (64%) with the cost of thalidomide accounting for 56% of the overall difference (table 3). Post-progression therapy accounted for 21% of the overall difference (table 3); this finding was largely attributable to the difference in the cost of lenalidomide-based therapy (16 [25%] of 62 patients in the thalidomide group vs ten [12%] of 84 patients in the control group—ie, the higher proportion of patients using lenalidomide in the thalidomide group led to a higher cost for lenalidomide in that group), and that 50% of the control group went on to receive thalidomide-based treatment after relapse. Use of zoledronic acid contributed 15% to

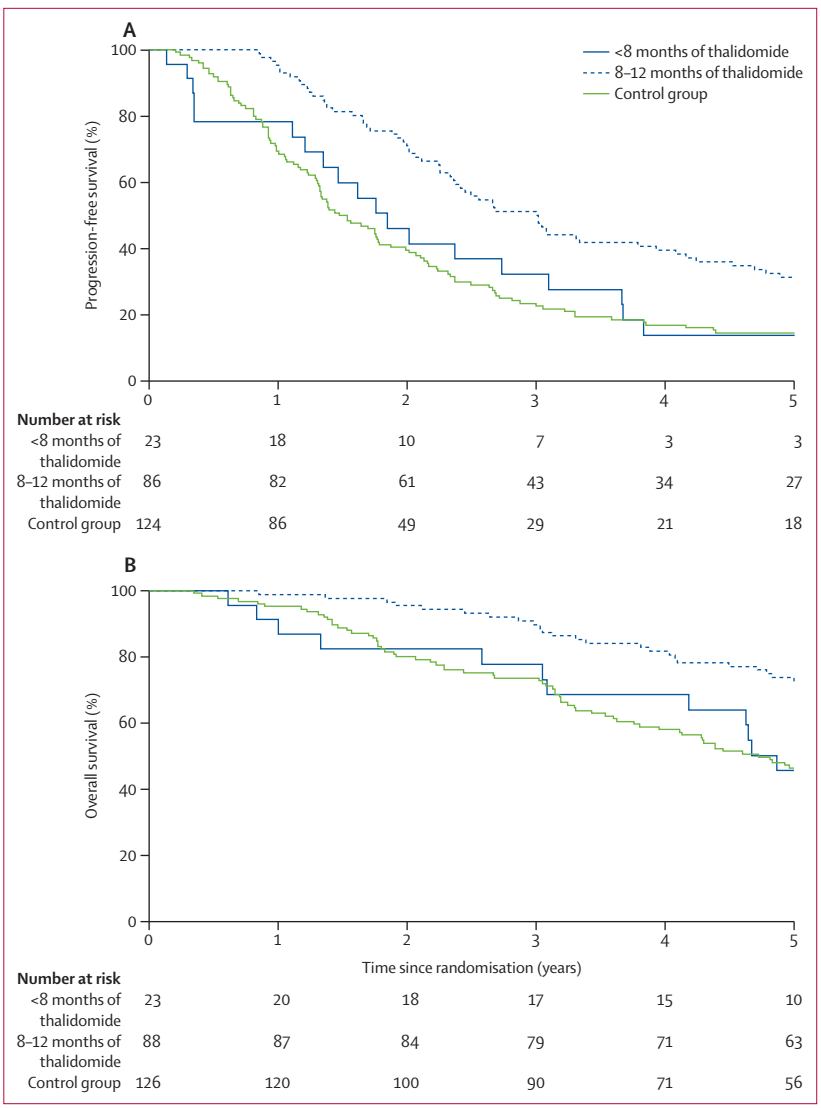

Figure 3: **Kaplan-Meier curves showing progression-free survival (A) and overall survival (B) by duration of thalidomide exposure**

	Thalidomide group (n=42)	Control group (n=54)
Bortezomib based		
Responder	4 (50%)	7 (58%)
Non-responder	4 (50%)	5 (42%)
Lenalidomide based		
Responder	10 (77%)	8 (80%)
Non-responder	3 (23%)	2 (20%)
Thalidomide based		
Responder	5 (63%)	18 (75%)
Non-responder	3 (38%)	6 (25%)
Other (trial, alkylator, radiotherapy)		
Responder	7 (54%)	4 (50%)
Non-responder	6 (46%)	4 (50%)
Total		
Responder	26 (62%)	37 (69%)
Non-responder	16 (38%)	17 (32%)

Data are n (%). We defined responders as patients who had a partial response, a very good partial response, or a complete response. We defined non-responders as patients who had a minor response, stable disease, or progressive disease.

***Table 2*: Response to salvage therapy**

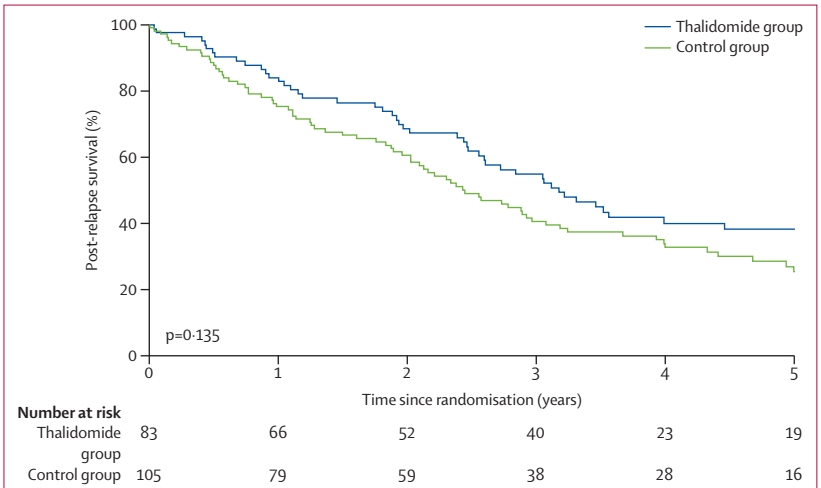

***Figure 4*: Post-relapse survival by treatment group**

	Thalidomide group	Control group	Difference
Primary drug therapies	23 414	7434	15 981
Thalidomide	13 983	0	13 983
Zoledronic acid	9263	7284	1975
Prednisolone	169	147	22
Post-relapse therapies	24 857	19 589	5268
Lenalidomide	12 086	5854	6232
Bortezomib	6209	4812	1397
Thalidomide	2201	5971	−3770
Other	4361	2951	1410
Medical and associated services	16 953	14 094	2859
Serious adverse events	2 687	1 883	804
Total costs	67 911	42 999	24 912

***Table 3*: Incremental costs for the average patient (AUS$)**

the incremental cost between the thalidomide and control groups (as both a primary therapy and medical service for infusion). This difference is due to the longer duration of freedom from progression, and hence longer overall survival, in patients in the thalidomide group than in those in the control group, resulting in more time on zoledronic acid treatment. Overall, the mean number of infusions of zoledronic acid was higher in patients in the thalidomide group than in those in the control group (21·39 *vs* 16·49). Notably, serious adverse events were the smallest contributor to the difference in incremental cost (3%; table 3).

When combined with the discounted mean life-year gained in survival, the resulting incremental cost-effectiveness ratio (ICER) was $26 996 per mean life-year gained for the thalidomide group compared with the control group. Subsequent analyses showed that this result was most sensitive to the estimated gain in survival (with use of the upper and lower 95% CIs the ICERs were $16 362 and $77 098, respectively) and to assumptions regarding the manner in which post-progression therapy costs were included (eg, assuming that patients in both groups who progressed received all three therapies in the same sequence reduced the ICER to $9731). The results were robust to variations in assumptions about the costing of serious adverse events, treatment compliance, the inclusion of wastage, infusion costing, and the discount rate (data not shown).

Discussion

Our results recapitulate our previous findings in that progression-free survival and overall survival benefits with thalidomide and prednisolone consolidation after autologous stem-cell therapy at a median of 3 years after randomisation are durable 5 years after randomisation. Although this findings might be in contrast to those from several other studies,[11–13] our updated results for overall survival are consistent with the meta-analysis done by the Medical Research Council group,[13] which showed a significant late benefit in overall survival (7 year difference HR 12·3, 95% CI 5·5–19·0; p<0·001).

The major factor enabling the translation of the observed progression-free survival benefit into an overall survival benefit was the absence of disadvantage at the time of relapse, in terms of both overall response rate to salvage therapy and post-relapse survival. Again, this finding is consistent with reports by the IFM group,[14] with thalidomide monotherapy as maintenance after tandem autologous stem-cell transplantation. However, other reports[11,12,15] have shown that survival after first disease progression was longer in patients who had not received maintenance thalidomide than in those who had. We considered whether preferential use of alternative novel drugs at first relapse might have provided an advantage to patients in the thalidomide group; however, response rates to salvage therapy were similar between groups. Use of thalidomide as salvage therapy was similarly effective

in each study group, arguing against a deleterious effect of previous exposure. Importantly, median progression-free survival in the thalidomide group was 1·7 years longer than the median duration of thalidomide exposure, that is, most patients were no longer on thalidomide consolidation at the time of progression. We conclude that because post-relapse survival did not differ between the treatment groups, a short duration of thalidomide after autologous stem-cell transplantation is not associated with development of resistant disease.

Recommendations for a specific duration of thalidomide consolidation therapy have been difficult to make. Median time to discontinuation in several trials was significantly shorter than the time scheduled, mainly because of toxic effects: 7 months in the MRC MMIX study[13] (intended to continue indefinitely), 15 months in the IFM 99-02 study[14] (indefinite), 16 months in the NCIC-CTG MY.10 study[11] (intended for 48 months) and 24 months in the HOVON 50 study[12] (indefinite). Barlogie and colleagues[15] previously reported no effect of thalidomide duration on clinical outcomes after reiterative landmark analyses in the TT2 study. However, our post-hoc landmark analyses suggest that only a short duration of thalidomide and prednisolone consolidation therapy after autologous stem-cell transplantation might confer survival benefit, consistent with recommendations from the International Myeloma Working Group to limit post-transplantation thalidomide to 12 months or less to reduce toxic effects.[16]

We are not aware of any other randomised trial assessing the cost-effectiveness of thalidomide after autologous stem-cell transplantation, nor has this been previously established for Australian clinical practice. However, although the present analysis was comprehensive in that it encompassed treatment exposure from initiation of consolidation to progression and beyond, we do acknowledge its limitations. First, these data are only strictly applicable to an Australian health-care setting, but extrapolation to jurisdictions with similar models of health-care funding is reasonable. Second, although these data cannot be directly compared with cost-effectiveness ratios in terms of cost per quality-adjusted life-year (QALY), they do validate the availability of thalidomide within a publicly funded health-care system such as that in Australia, and might help inform patients faced with the prospect of self-funding their own treatment. Specifically, the ICER of $26 996 per life-year gained is comparatively low compared with the cost of other pharmaceutical drugs approved for funding by the Australian Pharmaceutical Benefits Advisory Committee because, historically, new medicines submitted for subsidy via the Pharmaceutical Benefits Scheme, with a ratio in the range of $45 000–$75 000 per QALY, have an increased chance of being considered favourably by the committee.[17,18]

With an incremental cost of $24 912, a QALY gain of 0·55 would produce a cost per QALY of $45 000. The life-years gained in our analysis were 0·92. In this context, a QALY gain of 0·55 might not be unreasonable. However, we did not assess patients' quality of life. Evidence from the use of thalidomide in a similar setting, albeit with the likelihood of a significantly greater cumulative dose of thalidomide than in our study, would indicate a decrement in quality of life associated with the occurrence of treatment-related side-effects.[11] Such evidence should be weighed against prolongation of longevity and improvements in quality of life due to the absence of disease progression and therefore a prolonged treatment-free interval before the start of second-line therapy. Harris and colleagues[18] suggest that claims of cost-effectiveness are likely to be supported in the presence of life-threatening disorders or with strong evidence of a clinical effect. Both scenarios apply to the case of thalidomide after autologous stem-cell transplantation. Finally, we did the cost-effectiveness analysis retrospectively. Although a prospective analysis would have been preferable, we have estimated resource use in a consistent manner for both treatment groups and provided a reasonable assessment of the cost-effectiveness of consolidation treatment, including treatment of adverse

Panel: Research in context

Systematic review

In 2002, the standard of care for multiple myeloma in young, otherwise healthy patients in Australasia was autologous stem-cell transplantation; however, relapse was inevitable, with few therapeutic opportunities available at the time of relapse. In the 3 previous years, thalidomide had been shown to have activity in patients with multiple myeloma who relapsed after autologous stem-cell transplantation,[21] and further studies[22,23] confirmed synergistic anti-multiple myeloma activity in relapsed disease when thalidomide was combined with corticosteroids. Furthermore, that year, the SWOG trial[24] assessing alternate-day prednisone maintenance confirmed the tolerability and effectiveness of such an approach in patients with multiple myeloma who had previously had conventional chemotherapy. On the basis of these data, we postulated that the combination of thalidomide and corticosteroids might confer survival benefit when used after autologous stem-cell transplantation. However, because of concerns about drug cost, toxic effects, and the theoretical possibility of generation of resistant disease, we elected to pursue a post-transplantation consolidation strategy with a restricted duration of thalidomide exposure, rather than an indefinite maintenance approach. No data existed at the time of initiation of the ALLG MM6 trial to describe the use of thalidomide as a pre-planned strategy after autologous stem-cell transplantation.

Interpretation

This final report of the ALLG MM6 trial confirms the long-term progression-free survival and overall survival benefit achieved with a planned 12-month duration of thalidomide and prednisolone after autologous stem-cell transplantation, compared with prednisolone alone. Importantly, such an approach was not associated with shortened post-relapse survival or any increase in the risk of second primary malignancies. Furthermore, the cost associated with such an approach, although calculated in the context of the Australian health system, was very modest. Although use of thalidomide has been largely supplanted by the newer novel drugs bortezomib and lenalidomide in early phases of multiple myeloma in high-income nations, the reality for most patients globally is that such drugs are frequently inaccessible or unaffordable, and thalidomide continues to be widely used. We hope our findings will encourage the ongoing appropriate use of thalidomide post-autologous stem-cell transplantation in combination with corticosteroids for the forseeable future until, hopefully, more effective, tolerable, and affordable alternatives become available.

events and post-progression care in patients who have undergone transplantation.

The cost of the post-transplantation drug therapy was the largest contributor to the ICER, with thalidomide accounting for more than half of this cost. However, this result would compare favourably with the potential alternative strategy using lenalidomide. The published cost for 1 month of lenalidomide at a dose of 10–15 mg per day (dose as per IFM 2005-02[19] and CALGB 100104[20]) in Australia is more than 4·5 times the cost of thalidomide dosed at 200 mg per day ($7586·61–$8775·48 *vs* $1680), which suggests that a much bigger ICER would result should indefinite (or indeed similar fixed-duration) lenalidomide be substituted for fixed-duration thalidomide. Moreover, published clinical trial data and published consensus statements and therapeutic guidelines informed by these data, in the era of novel therapeutics have little relevance to many patients with multiple myeloma and their carers when a global perspective is considered. Outside North America and western Europe, access to and affordability of both bortezomib and lenalidomide is restricted, particularly for the latter drug. By contrast, thalidomide is widely available, affordable, and used in Australasia, east Asia, southeast Asia, eastern Europe, and South America, including as a strategy after autologous stem-cell transplantation (panel). As such, we feel that in real terms, data for the cost-effective and safe use of thalidomide remain relevant in 2014, and will continue to do so in the foreseeable future. This theory gives weight to the results of this final analysis of the ALLG MM6 study and supports their potential importance in guiding clinical practice in the management of transplant-eligible patients with multiple myeloma, particularly in the absence of other available therapies after autologous stem-cell transplantation, such as lenalidomide.

Contributors

ASp conceived and designed the trial. ASp, HMP, AWR, and KB contributed patients. AK, ASm, and NK obtained and assembled data. AK, RDAL, CF, and ASp analysed the data and constructed the figures. AK wrote the first version of the report. AK, RDAL, CF, and ASp wrote the final version of the report. All authors approved the final draft of the report.

Declaration of interests

We have no competing interests.

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