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Thalidomide maintenance following high-dose melphalan with autologous stem cell support in myeloma

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Abstract

Background—Recent experience with thalidomide maintenance after high-dose chemotherapy with autologous stem cell support has demonstrated improvement in progression-free and overall survival. We further explored the tolerability and efficacy of lower doses of maintenance thalidomide in this single institution study.

Patients and Methods—Thirty-eight myeloma patients were enrolled and treated with melphalan 200 mg/m² followed by autologous stem cell transplant. Thalidomide 50 mg/day was started on day ≥60 after recovery of blood counts and escalated to a maximum dose of 200 mg/day. Responses were assessed at 2 months, 1 year, and 2 years post-transplant.

Results—Of the 38 enrolled patients, 7 patients never received thalidomide. Among 31 patients receiving thalidomide, complete or very good partial responses were observed in 65% and 42% of patients at 1 and 2 years, respectively. Tolerability was a major issue, with only 17 patients completing 1 year of thalidomide. The goal dosing of 200 mg/day was achieved in just 17/31 patients, and the median tolerated thalidomide dose was 100 mg/day. Sensory neuropathy was the primary reason for dose modification and discontinuation. No thromboembolic events were observed. Median progression-free survival was 20.8 months and the median overall survival was more than 60 months.

Conclusion—Thalidomide maintenance at a goal dose of 200 mg/day was not feasible in this population, with our data suggesting that 100 mg/day is a more reasonable maintenance dose.

Keywords

thalidomide; transplant; myeloma; melphalan; neuropathy; chemotherapy

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Introduction

Previous experience with high-dose melphalan combined with autologous stem cell support has demonstrated improved response rates, event-free survival, and overall survival in patients with multiple myeloma.^{1,2} In addition, novel agents such as thalidomide have emerged as therapeutic options in the treatment of relapsed, refractory disease,³⁻⁵ and more recently in upfront therapy for myeloma.⁶⁻⁸ Ongoing interest has centered on the use of thalidomide for management of minimal residual disease post-transplant. Recent experience with thalidomide maintenance after autologous stem cell transplant has shown improvements in event-free and overall survival.⁹⁻¹¹ However, there is still much to understand about the optimal dosing and duration of thalidomide in the post-transplant setting. This study was developed to determine the tolerability and efficacy of thalidomide maintenance therapy following high-dose melphalan with autologous stem cell support in patients with multiple myeloma.

Patients and methods

Patients

Patients between 18 and 70 years of age with newly diagnosed and relapsed multiple myeloma were eligible for treatment. Patients were required to have evidence of marrow plasmacytosis, lytic bone lesions, and measurable monoclonal serum and/or urine protein to be eligible for enrollment. Patients meeting criteria for smoldering myeloma, MGUS, or solitary plasmacytoma were excluded from participation. Additional requirements included that patients have an ECOG performance status of ≤ 1 , not be pregnant or breast-feeding, and have no history of prior malignancies (with the exception of basal cell carcinomas and treated solid tumors without evidence of recurrence for ≥ 5 years). Patients could not have active or uncontrolled infections (including known HIV infection or chronic hepatitis B or C infection) or other uncontrolled medical conditions. Adequate organ function was required as demonstrated by a serum creatinine of $\leq 2 \times 10^{-2}$ g/L and a creatinine clearance of $\geq 5 \times 10^{-2}$ L/minute, a total bilirubin of $\leq 2.5 \times 10^{-2}$ g/L, and an AST < 3 times the upper limits of laboratory normal. Adequate cardiac function was defined as a resting ejection fraction of $\geq 45\%$. Adequate pulmonary function was defined as a diffusion capacity $\geq 50\%$ of predicted, FEV₁ $\geq 50\%$ of predicted, and pO₂ ≥ 60 mm Hg. Prior treatment with thalidomide was not exclusionary.

The study was approved by the Human Subjects Committee and Institutional Review Board at the University of Wisconsin Hospital and Clinics. All patients signed an informed consent document describing the investigational nature of the proposed treatments.

Treatment

At the time of study enrollment, patients underwent procurement of autologous peripheral blood stem cells. The minimum endpoint for peripheral stem cell collection was 3×10^6 CD34⁺ cells/kg, with an ideal range of $5-10 \times 10^6$ CD34⁺ cells/kg. Administration of high-dose chemotherapy and infusion of autologous stem cells were performed in the inpatient setting. Melphalan 200 mg/m² was administered intravenously on day -2 pre-transplant, and patients then received re-infusion of their stem cell product on day 0. Patients received G-CSF beginning day +5 post-transplant, and continued daily G-CSF until the absolute neutrophil count exceeded 5×10^4 cells/L for 2 consecutive days. Patients received anti-infective prophylaxis with acyclovir, fluconazole, and trimethoprim/sulfamethoxazole. Pamidronate 90 mg was administered intravenously monthly to all patients starting day +100 post-transplant.

Thalidomide was started ≥ 60 days post-transplant in patients without evidence of progression who had recovery of blood counts. Patients were required to have adequate engraftment with absolute neutrophil counts $\geq 750/\mu\text{L}$ and platelets $\geq 20,000/\mu\text{L}$ prior to starting thalidomide. Patients started thalidomide at a dose of 50 mg/day, and doses of thalidomide were escalated in 50 mg increments every 2 weeks as tolerated to a maximum dose of 200 mg/day. Patients who required a dose-reduction of thalidomide for an adverse event thought possibly attributed to thalidomide were allowed to later re-escalate the dose of thalidomide. Patients without evidence of progression who were able to tolerate thalidomide completed 1 year of maintenance therapy. Patients were not required to receive prophylactic anticoagulants while receiving thalidomide.

Laboratory evaluation

Evaluation at baseline included a serum immunoglobulin profile (serum protein electrophoresis, quantitative immunoglobulins, and kappa:lambda ratio), urine immunoglobulin profile (24 hour urine collection for total protein, creatinine clearance, urine protein electrophoresis), and serum and urine immunofixation. Assessments of serum and urine immunoglobulin profiles and immunofixation were repeated at 2 months, 6 months, 9 months, 12 months, and yearly thereafter. A skeletal survey and bone marrow biopsy with cytogenetic analysis were required at baseline, at 2 months post-transplant, 1 year post-transplant, and then annually thereafter.

Routine CBC with differential and chemistries were repeated at least weekly until patients were transfusion-independent, and then every 2-4 weeks until at least day +100 post-transplant. Patients also underwent testing for hepatitis B and C status and baseline viral serologies (CMV, HIV, syphilis) at study entry. Baseline cardiac and pulmonary testing was performed with echocardiography or multiple gated acquisition scanning and pulmonary function testing. Women of child-bearing potential required a pregnancy test at enrollment, at 2 months post-transplant, then monthly while taking thalidomide.

Criteria for response and relapse

The response criteria as defined by the European Group for Blood and Marrow Transplantation were used in this study,¹⁰ with the addition of a very good partial remission (VGPR) criteria.¹¹ A complete response (CR) was defined as the disappearance of monoclonal protein on urine and serum immunofixation and $\leq 5\%$ plasma cells on bone marrow biopsy. A VGPR required a $\geq 90\%$ reduction in the monoclonal serum protein from the pre-treatment value. A partial response (PR) was defined as $\geq 50\%$ reduction in the serum paraprotein level or a 90% decrease in the level of monoclonal urine light chains. Minimal response (MR) was defined as a 25% decrease in the serum paraprotein level, and stable disease (SD) included patients who did not meet the criteria for a PR or progression. Progressive disease (PD) was defined as $\geq 25\%$ increase in serum paraprotein level. *Relapse* after a CR was defined by the reappearance of a monoclonal protein in serum or urine or recurrence of bone marrow infiltration in a patient with a prior CR.

Statistical analysis

The primary objectives of this study were to assess the complete or very good partial response rates at 1 year post-transplant and to assess the progression-free survival of patients with multiple myeloma treated with high-dose melphalan and post-transplant thalidomide maintenance therapy. Secondary objectives included assessment of thalidomide's ability to improve the level of response after transplant (i.e., convert a CR to a PR, ect.) and evaluation of the toxicities associated with thalidomide maintenance therapy in the post-transplant setting. Descriptive statistics were used to characterize patients enrolled in this trial. Response rates were reported for all patients treated with thalidomide at 2 months, 1

year, and 2 years post-transplant. Progression-free survival and overall survival curves for the intention to treat population were estimated using the Kaplan-Meier method. Progression-free survival was defined as the time from the day of transplant (re-infusion of autologous stem cells) to the first date of progression of disease or death. Patients were censored at the date the patient was last known to have stable but not progressive disease if alive. Overall survival was defined as the time from the day of transplant to the date of death or the date last known to be alive.

Descriptive data is provided on the number of patients requiring dose reductions and the median duration and doses of thalidomide tolerated. Toxicities with thalidomide are described as well.

Results

Patients

Between May 7, 2001, and March 2, 2005, 38 patients were enrolled. Baseline characteristics of the patients are shown in Table 1. In the enrolled patient population, the median age was 60 (range 39-70), and 92% of patients had Durie-Salmon stage II or III disease at diagnosis. Nine (24%) of the enrolled patients had previously been treated with thalidomide for a median of 5.3 months (range 0.7-12.0 months). Eleven patients (29%) had relapsed or refractory disease at the time of autologous transplantation. Cytogenetic abnormalities were present in 21% (n=8) of patients at enrollment. Five patients had complex cytogenetics present at enrollment, with 2 of these patients demonstrating the adverse cytogenetic abnormality deletion of chromosome 13. The median time from diagnosis to transplant was 7.3 months (range 4.2-47.6 months). None of the enrolled patients had a serum creatinine $\geq 2 \times 10^{-2}$ g/L at the time of study entry.

For comparison, the baseline characteristics of the 31 patients who actually received thalidomide (evaluable study group) are summarized in Table 1. There are not major differences between the enrolled patient population and the evaluable group. However, fewer patients in the evaluable group were previously treated with thalidomide, and none of the evaluable study group had deletion of chromosome 13.

Responses

Seven patients never received thalidomide, leaving 31 patients evaluable for response. Responses were reported in this evaluable study group at intervals of 2 months, 1 year, and 2 years post-transplant (Table 2). At both 2 months and 1 year post-transplant, 65% of patients had evidence of CR or VGPR. By 2 years post-transplant, 42% of the evaluable study group were in CR or VGPR.

Eleven events of response improvements were observed in 10 patients (32%) while receiving maintenance thalidomide, including 1 patient who demonstrated 2 events of response improvement at both the 1 year and 2 year assessments. Nine of the improved response events were observed between 2 months and 1 year post-transplant, and the remaining 2 events of improved response occurred between 1 and 2 years. The observed events of improvement in response included: VGPR improved to CR (n=3); PR improved to VGPR (n=4); and SD improved to CR (n=1), VGPR (n=2), or PR (n=1). All but 1 of the 10 patients demonstrating an improvement in response with thalidomide had received thalidomide ≥ 10 months.

Only 1 of the 7 patients (14%) who did not receive thalidomide demonstrated an improved response, with an improvement from a VGPR to a CR between 2 months and 1 year post-transplant. Of the 7 patients who never received thalidomide, 1 patient was lost to follow-up,

1 died from sepsis and multi-organ failure on day +11 post-transplant, and 1 patient had PD at 2 months and died during the first year post-transplant. The 4 remaining patients who never received thalidomide were noted to have evidence of VGPR (n=3) or SD (n=1) at 2 months.

Tolerability of thalidomide

Seven patients never received thalidomide for reasons including early progression (n=1), early toxic death (n=1), failure to engraft (n=1), and patient refusal (n=4). The majority of patients were not able to tolerate the goal thalidomide dose of 200 mg/day, with sensory neuropathy as the most common reason for thalidomide intolerance. The median tolerated dose of thalidomide was 100 mg/day. Seventeen (55%) of the 31 patients who received thalidomide successfully completed at least 1 year of therapy. Eleven patients continued thalidomide for >1 year (median of 18.9 months), with the decision for continuation of therapy beyond the 1 year specified by the protocol based on physician and/or patient preference.

Of the patients who received thalidomide but did not complete 1 year of therapy, thalidomide was given for a median duration of 5.2 months. Progressive disease was the most common reason for early discontinuation of therapy (n=5). Other indications for early discontinuation of thalidomide included sensory neuropathy (n=4), rash (n=3), fatigue (n=1), and mucositis (n=1). Dose modifications of thalidomide were required in 19 patients (61%), including 3 patients with early discontinuation of thalidomide as their first dose modification.

Toxicity with thalidomide

Toxicity data are reported according to the CTCAE version 3.0. Sensory neuropathy was the most common reason for dose modification (10/19), but with only 1 event of grade 3 sensory neuropathy reported. Constipation and fatigue were common, but there were no grade ≥ 3 events reported. One patient experienced grade 3 hypertension while receiving thalidomide, but had a pre-existing history of hypertension requiring multiple medications. Four events of grade 3 or 4 infections occurred in the absence of neutropenia during therapy with thalidomide. Three of the events occurred in the same patient who developed influenza requiring mechanical ventilation followed by hospitalizations for community acquired pneumonia and *Streptococcal pneumoniae* sepsis. Two other patients were hospitalized, one with *Pneumocystis carinii* pneumonia and the other with community-acquired pneumonia. One patient who had developed a rash during pre-transplant therapy with thalidomide developed a grade 3 rash with thalidomide rechallenge. There were no thromboembolic complications reported during treatment with thalidomide despite the omission of prophylactic anticoagulants.

Hematologic toxicities with thalidomide were manageable. Only 2 events of grade 3 and 4 thrombocytopenia occurred during treatment with thalidomide. One event of grade 4 thrombocytopenia occurred in a patient with poor graft function prior to therapy with thalidomide. No patient required discontinuation of thalidomide for hematologic toxicities. Toxicity data are shown in Table 3.

Survival

Measures of survival outcomes are reported for the intention to treat population. As of April 1, 2007, 30 patients have experienced an event, including 14 deaths and 16 patients who remain alive after experiencing progression. Eight patients remain alive without evidence of progression. The median duration of follow-up for the enrolled study population is 35.7 months (range 0.4-64.1). Median overall survival is greater than 5 years. At 2 and 3 years

post-transplant, overall survival rates of 81% and 72% were observed, respectively. The observed median PFS in the enrolled study group was 20.8 months (Figure 1). At 2 and 3 years post-transplant, the rates of progression-free survival were 61% and 33%, respectively.

Discussion

High-dose chemotherapy with autologous peripheral stem cell support remains a standard therapy in younger patients and selected older patients with multiple myeloma. This therapeutic approach is associated with high response rates and prolonged durations of remission, but is ultimately a non-curative therapy. Maintenance therapy following autologous transplant remains an area of interest with the goal of delaying relapse. Thalidomide is an attractive agent for use in the maintenance setting because of the convenience of its oral dosing as well as its novel mechanisms of action.

The benefit of maintenance thalidomide was confirmed by the results of IFM 99-02, in which 597 myeloma patients were randomized following tandem autologous transplants to maintenance therapy with either pamidronate alone, pamidronate + thalidomide, or observation.⁹ Thalidomide administered for one year post-transplant improved the rate of response, and patients treated with maintenance thalidomide were observed to have a statistically significant improvement in event-free survival ($p=.002$), relapse-free survival ($p=.003$), and overall survival ($p=.04$).⁹ In addition, the experience by a group of Tunisian investigators recently reported an improvement in 3 year overall and progression-free survival with a 6 month course of thalidomide following a single autologous transplant in comparison with a randomized group receiving double autologous transplants for newly-diagnosed myeloma.¹⁰ Similarly, a large retrospective review of patients undergoing autologous stem cell transplant for myeloma at Emory University found that patients receiving post-transplant thalidomide had an improved median survival compared with patients who had not received thalidomide (65.5 months versus 44.5 months) and improved overall survival compared with patients who received thalidomide at relapse.¹¹

Therefore the existing literature strongly supports the notion of clinical benefit for thalidomide administration following autologous transplantation. What is less clear is the optimal dose and schedule. Attal *et al* in IFM 99-02 observed a mean tolerated dose of thalidomide of 200 mg/day despite a planned targeted maintenance dose of 400 mg/day. Only 30 patients (15%) in IFM 99-02 were able to tolerate the planned dose of thalidomide 400 mg/day for a median of 21 months.⁹ In a Canadian trial of 67 myeloma patients randomized post-transplant to 200 mg versus 400 mg of daily thalidomide, a maintenance dose of 400 mg/day was found to be significantly more toxic with higher rates of drug discontinuation.¹⁴ Among patients randomized to 400 mg/day of thalidomide, 36% of patients experienced grade 3 or 4 toxicities, and only 41% of patients remained on thalidomide at 18 months. By comparison, 27% of patients treated with 200 mg/day of thalidomide experienced grade 3 or 4 toxicities and 76% of patients remained on thalidomide at 18 months.

Our data suggest that even 200 mg/day is intolerable for many patients, and 100 mg/day of thalidomide may be a more reasonable goal for maintenance therapy. The reason for the lower thalidomide dose tolerance observed in our data may be related to several factors, including previous exposure to thalidomide (24% of enrolled patients had previously received thalidomide), a significant portion of patients with relapsed or refractory disease at the time of transplant (29%), lower tolerance for toxicities when thalidomide is given as maintenance therapy following autologous transplant, and a potential selection bias in our population which is more representative of a community practice rather than a large myeloma referral center. In addition, there may be individual differences in drug metabolism

leading to thalidomide intolerance (e.g., sensory neuropathy), and a better understanding of the role of pharmacogenomics in thalidomide metabolism may identify patients at higher risk of adverse effects from thalidomide.¹⁵ However, as these data are more representative of patient populations treated in community-based practices that constitute the majority of myeloma patients undergoing therapy, insight can be gained into the efficacy and tolerability of thalidomide at lower dosing levels.

Maintenance therapy with lower doses of thalidomide may be an effective alternative based on previous experience with thalidomide at doses less than 200 mg/day. For example, other groups have reported activity with thalidomide at doses as low as 50-100 mg/day.^{10,16-18} Abdelkefi *et al* reported excellent tolerability of thalidomide 100 mg/day administered for 6 months following a single autologous transplant. Rates of all grade ≥ 3 toxicities were less than 5% of adverse events, including peripheral neuropathy, fatigue, and constipation.¹⁰ An Australian randomized study of single autologous transplantation followed by maintenance with either thalidomide or thalidomide and alternating day prednisolone found that 64% of patient were able to tolerate 12 months of thalidomide, but at a median dose of 100 mg despite a planned dose of 200 mg.¹⁶ Similarly, a non-inferiority study of high versus low-dose thalidomide (400 mg versus 100 mg) in patients with relapsed and refractory myeloma (IFM 01-01) found no difference in 1 year survival between the groups.¹⁷ Patients randomized to receive high-dose thalidomide ultimately received a median dose of 200 mg/day, and thalidomide 100 mg/day was better tolerated with significantly less high-grade sedation, constipation, and sensory neuropathy ($p < .001$). Based on these and other data, further consideration of maintenance thalidomide at lower targeted doses is reasonable.

Other agents such as the thalidomide analogue lenalidomide are under investigation as alternative maintenance therapies post-transplant, with particular interest as to whether improved benefit or reduced toxicity can be achieved. For example, ECOG/CALGB 100104 is a phase III placebo-controlled trial evaluating the efficacy of maintenance lenalidomide following autologous transplant in newly diagnosed myeloma.¹⁸ In addition, recent use of a maintenance strategy with thalidomide and alternate day prednisolone demonstrated improved 2 and 3 year progression-free and overall survival compared with thalidomide alone following a single autologous transplant.¹⁶ However, until alternative maintenance strategies demonstrate a proven role in myeloma, ongoing consideration of tolerable and effective dosing strategies of thalidomide remains an important goal in improving outcomes following autologous transplantation in myeloma.

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References

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996;335:91–7. [PubMed: 8649495]
2. Attal M, Harousseau JL. Standard therapy versus autologous transplantation in multiple myeloma. *Hematol Oncol Clin North Am* 1997;11:133–46. [PubMed: 9081208]
3. Munshi NC, Desikan KR, Barlogie B. Clinical experience with thalidomide in multiple myeloma: phase II trial results in refractory disease and ongoing studies. *Semin Hematol* 2000;37:15–21.
4. Alexanian R, Weber D. Thalidomide for resistant and relapsing myeloma. *Semin Hematol* 2000;37:22–5. [PubMed: 10676920]
5. Zomas A, Anagnostopoulos N, Dimopoulos MA. Successful treatment of multiple myeloma relapsing after high-dose therapy and autologous transplantation with thalidomide as a single agent. *Bone Marrow Transplant* 2000;25:1319–20. [PubMed: 10871741]

6. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2006;24:431–6. [PubMed: 16365178]
7. Palumbo A, Bertola A, Musto P, Caravita T, Callea V, Nunzi M, et al. Oral melphalan, prednisone, and thalidomide for newly diagnosed patients with myeloma. *Cancer* 2005;104:1428–33. [PubMed: 16116606]
8. Facon T, Mary J, Harousseau J, Huguier F, Berthou C, Grosbois B, et al. Superiority of melphalan-prednisone (MP) + thalidomide (THAL) over MP and autologous stem cell transplantation in the treatment of newly diagnosed elderly patients with multiple myeloma. *J Clin Oncol* 2006;24(Suppl 18) 1s (abstr. 1).
9. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma (IFM 99 02). *Blood* 2006;108:3289–94. [PubMed: 16873668]
10. Abdelkefi A, Ladeb S, Torjman L, Othman TB, Lakhal A, Romdhane NB, et al. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. *Blood* 2008;111(4):1805–10. [PubMed: 17875806]
11. Brinker BT, Waller EK, Leong T, Heffner LT Jr, Redei I, Langston AA, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. *Cancer* 2006;106:2171–80. [PubMed: 16598756]
12. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. *Br J Haematol* 1998;102:115–23.
13. Durie BGM, Harousseau J-L, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006;20:1467–73. [PubMed: 16855634]
14. Stewart AK, Chen CI, Howson-Jan K, White D, Roy J, Kovacs MJ, et al. Results of a multicenter randomized phase II trial of thalidomide and prednisone maintenance therapy for multiple myeloma after autologous stem cell transplant. *Clin Cancer Res* 2004;10:8170–76. [PubMed: 15623591]
15. Richardson P, Hideshima T, Anderson K. Thalidomide: emerging role in cancer medicine. *Annu Rev Med* 2002;53:629–57. [PubMed: 11818493]
16. Spencer A, Prince HM, Roberts A, Bradstock K, Prosser I. Thalidomide improves survival when used following ASCT. *Haematologica* 2007;92(Suppl 2):41-2. (abstr. S7b.5).
17. Yakoub-Agha I, Doyen C, Hulin C, Marit G, Voillat L, Grosbois B, et al. A multicenter prospective randomized study testing non-inferiority of thalidomide 100 mg/day as compared with 400 mg/day in patients with refractory/relapsed multiple myeloma: results of the final analysis of the IFM 01-02 study. *J Clin Oncol* 2006;24(Suppl 18):427s. abstr. 7520.
18. Durie BGM, Stepan DE. Low dose thalidomide alone and in combination: long-term follow-up. *Blood* 2001;98:163a. abstr. 688.
19. National Cancer Institute (www.clinicaltrials.gov). Lenalidomide in treating patients who are undergoing autologous stem cell transplant for multiple myeloma: NCT00114101, ECOG/CALGB 100104 (ongoing trial).

Figure 1.

Kaplan-Meier curves for progression-free and overall survival.

Kaplan-Meier plots of progression-free and overall survival post-transplant (n=38). Bars indicate 95% confidence intervals.

Table 1

Baseline patient characteristics.

	Enrolled patients (n=38)	Evaluable group treated with thalidomide (n=31) ¹
Median age	60	60
Age ≥ 65	8 (21%)	7 (23%)
Female sex	17 (45%)	13 (42%)
IgA isotype	15 (39%)	11 (35%)
β ₂ microglobulin ≥ 3.5 mg/L	11 (29%)	8 (26%)
Relapsed/refractory disease pre-transplant ²	11 (29%)	9 (29%)
Durie-Salmon stage (at diagnosis):		
Stage I	3 (8%)	2 (6%)
Stage II	10 (26%)	10 (32%)
Stage III	25 (66%)	19 (61%)
Median time from diagnosis to transplant	7.3 months	7.0 months
Cytogenetics: ³		
Not available	3 (8%)	3 (10%)
Normal	27 (71%)	21 (68%)
Abnormal	8 (21%)	7 (23%)
Complex ⁴	5 (13%)	4 (13%)
Deletion 13	2 (5%) ⁵	0
Prior thalidomide	9 (24%)	6 (19%)

¹ Includes all patients who received at least a single dose of thalidomide.

² Relapsed disease defined as documented progression followed at least a partial response to the most recent therapy; refractory disease defined as less than a partial response to the previous therapy.

³ Cytogenetic abnormalities are reported on all patients at the time of enrollment, as cytogenetics were retrospectively available in only 7 patients at the time of diagnosis; cytogenetic analysis included routine cytogenetics alone without confirmatory PCR or FISH analysis.

⁴ Complex cytogenetics defined as ≥2 cytogenetic abnormalities.

⁵ Both patients with deletion of chromosome 13 also had presence of complex cytogenetics and are included in the total number of patients with complex cytogenetic abnormalities.

Table 2

Responses in evaluable group treated with thalidomide (n=31).

	2 months ¹	1 year	2 years ²
CR	2 (6%)	3 (10%)	1 (3%)
VGPR	18 (58%)	17 (55%)	12 (39%)
PR	5 (16%)	4 (13%)	0
MR	0	0	0
SD	5 (16%)	1 (3%)	1 (3%)
PD	0	6 (19%)	10 (32%)
Died	0	0	5 (16%) ³

¹ One patient did not have data available at 2 months post-transplant.

² Includes 1 patient without response data available and 1 patient who is excluded after PD at 1 year (but still alive at 2 years).

³ Of the 5 patients who had died by 2 years, 4 patients had PD at 1 year and 1 patient had evidence of a VGPR at 1 year.

Table 3

Toxicity with thalidomide maintenance therapy.

Toxicity	N	Grade 1	Grade 2	Grade 3	Grade 4
Sensory neuropathy	18 ¹	12 (6)	5 (3)	1 (1)	0
Constipation	13	7	6 (2)	0	0
Fatigue	9	4 (1)	5 (3) ²	0	0
Rash	7 ³	4 (1)	2 (1)	1 (1) ⁴	0
Infection (without neutropenia)	6	0	1 (1) ⁵	3	2
Edema	3	2 (1)	1	0	0
Myalgias	3	2	1	0	0
Tinnitus	3	1	2 (1)	0	0
Depression	2	1 (1)	1 (1)	0	0
Hearing loss	2	0	2	0	0
Hypertension	1	0	0	1 (1)	0
Syncope	1	0	0	1	0
Mucositis	1	0	1 (1) ⁵	0	0
Other neurologic symptoms (TIA-like symptoms)	1	0	1 (1)	0	0
Leukopenia	17	8	9	0	0
Anemia	18	13	5	0	0
Thrombocytopenia	18	14	2	1	1

() Events requiring dose modification.

¹ Four of these sensory neuropathy events led to discontinuation of thalidomide (2 grade 1 events, 1 grade 3 event, 1 grade 4 event).² One event of grade 2 fatigue led to discontinuation of thalidomide.³ Three events of rash led to discontinuation of thalidomide.⁴ Event occurred in the setting of a patient who had experienced rash with prior thalidomide therapy.⁵ One patient experiencing recurrent grade 2 sinusitis and grade 2 mucositis discontinued thalidomide.