Original Contribution

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 survival (PFS) and overall survival (OS). We further explored the tolerability and efficacy of lower doses of maintenance thalidomide in this single-institution study. **Patients and Methods:** Thirty-eight patients with myeloma were enrolled and treated with melphalan 200 mg/m^2 followed by autologous stem cell transplantation. Thalidomide 50 mg per day was started on day ≥ 60 after recovery of blood counts and was escalated to a maximum dose of 200 mg per day. Responses were assessed at 2 months, 1 year, and 2 years after transplantation. **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 of dosing 200 mg per day was achieved in just 17 of 31 patients, and the median tolerated thalidomide dose was 100 mg per day. Sensory neuropathy was the primary reason for dose modification and discontinuation. No thromboembolic events were observed. The median PFS was 20.8 months, and the median OS was > 60 months. **Conclusion:** Thalidomide maintenance at a goal dose of 200 mg per day was not feasible in this population, with our data suggesting that 100 mg per day is a more reasonable maintenance dose.

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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 (EFS), and overall survival (OS) in patients with multiple myeloma (MM).[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 the management of minimal residual disease after transplantation. Recent experience with thalidomide maintenance after autologous stem cell transplantation (ASCT) has shown improvements in EFS and OS.[9-11] However, there is still much to understand about the optimal dosing and duration of thalidomide in the post-transplantation setting. This study was developed to determine the tolerability and efficacy of thalidomide maintenance therapy after high-dose melphalan with autologous stem cell support in patients with MM.

Patients and Methods

Patients

Patients aged between 18 years and 70 years with newly diagnosed and relapsed MM 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, monoclonal gammopathy of undetermined significance, or solitary plasmacytoma were excluded from participation. Additional requirements included that patients have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, not be pregnant or breast-feeding, and have no history of previous 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 ≤ 2×10^{-2} g/L

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and a creatinine clearance of ≥ 5×10^{-2} L per minute, a total bilirubin of ≤ 2.5×10^{-2} g/L, and an aspartate aminotransferase < 3 times the upper limits of laboratory normal. Adequate cardiac function was defined as a resting ejection fraction of ≥ 45%. Adequate pulmonary function was defined as a diffusion capacity ≥ 50% of predicted, forced expiratory volume in 1 second ≥ 50% of predicted, and pO_2 ≥ 60 mm Hg. Previous 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/m^2 was administered intravenously on day –2 before transplantation, and patients then received re-infusion of their stem cell product on day 0. Patients received granulocyte colony-stimulating factor (G-CSF) beginning day 5 after transplantation and continued daily G-CSF until their absolute neutrophil count (ANC) exceeded 500 cells/μL for 2 consecutive days. Patients received anti-infective prophylaxis with acyclovir, fluconazole, and trimethoprim/sulfamethoxazole. Pamidronate 90 mg was administered monthly to all patients starting day 100 after transplantation.

Thalidomide was started ≥ 60 days after transplantation in patients without evidence of progression who had recovery of blood counts. Patients were required to have adequate engraftment with ANC ≥ 750/μL and platelets ≥ 20,000/μL before starting thalidomide. Patients started thalidomide at a dose of 50 mg per day, and doses of thalidomide were escalated in 50 mg increments every 2 weeks as tolerated to a maximum dose of 200 mg per day. Patients who required a dose reduction of thalidomide for an adverse event (AE) 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 κ:λ 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 after transplantation, 1 year after transplantation, and then annually thereafter.

Routine complete blood count with differential and chemistries were repeated at least weekly until patients were transfusion independent, and then every 2-4 weeks until ≥ day 100 after transplantation. Patients also underwent testing for hepatitis B and C status and baseline viral serologies (cytomegalovirus, 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 childbearing potential required a pregnancy test at enrollment, at 2 months after transplantation, 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,[12] with the addition of a very good partial remission (VGPR) criteria.[13] A complete response (CR) was defined as the disappearance of monoclonal protein on urine and serum immunofixation and ≤ 5% plasma cells on bone marrow biopsy. A VGPR required a ≥ 90% reduction in the monoclonal serum protein from the pretreatment value. A partial response (PR) was defined as ≥ 50% reduction in the serum paraprotein level or a 90% decrease in the level of monoclonal urine light chains. Minimal response 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 ≥ 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 previous CR.

Statistical Analysis

The primary objectives of this study were to assess the complete or VGPR rates at 1 year after transplantation and to assess the progression-free survival (PFS) of patients with MM treated with high-dose melphalan and post-transplantation thalidomide maintenance therapy. Secondary objectives included assessment of thalidomide's ability to improve the level of response after transplantation (ie, convert a CR to a PR, etc) and evaluation of the toxicities associated with thalidomide maintenance therapy in the post-transplantation 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 after transplantation. Progression-free survival and OS curves for the intent-to-treat (ITT) population were estimated using the Kaplan-Meier method. Progression-free survival was defined as the time from the day of transplantation (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 transplantation to the date of death or the date last known to be alive. Descriptive

Table 1 Baseline Patient Characteristics

Characteristic	Enrolled Patients (N = 38)	Evaluable Group Treated with Thalidomide (n = 31)*
Median Age (Years)	60	60
Age ≥ 65 Years	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 Before Transplantation†	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 Transplantation	7.3 Months	7 Months
Cytogenetics‡		
Not available	3 (8%)	3 (10%)
Normal	27 (71%)	21 (68%)
Abnormal	8 (21%)	7 (23%)
Complex§	5 (13%)	4 (13%)
Del(13)	2 (5%)‖	0
Previous Thalidomide	9 (24%)	6 (19%)

*Includes all patients who received at least a single dose of thalidomide.
†Relapsed disease defined as documented progression followed by at least a PR to the most recent therapy; refractory disease defined as less than a PR to the previous therapy.
‡Cytogenetic abnormalities are reported on all patients at the time of enrollment because cytogenetics were retrospectively available in only 7 patients at the time of diagnosis; cytogenetic analysis included routine cytogenetics alone without confirmatory polymerase chain reaction or fluorescence in situ hybridization analysis.
§Complex cytogenetics defined as ≥ 2 cytogenetic abnormalities.
‖Both patients with del(13) also had presence of complex cytogenetics and are included in the total number of patients with complex cytogenetic abnormalities.
Abbreviation: Ig = immunoglobulin

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

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 years (range, 39-70 years), 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 months). Eleven patients (29%) had relapsed/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 (del[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 ≥ 2×10^{-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 del(13).

Table 2 Responses in Evaluable Group Treated with Thalidomide (n = 31)

Response	2 Months, n (%)*	1 Year, n (%)	2 Years, n (%)†
Complete Response	2 (6)	3 (10)	1 (3)
VGPR	18 (58)	17 (55)	12 (39)
Partial Response	5 (16)	4 (13)	0
Minimal Response	0	0	0
Stable Disease	5 (16)	1 (3)	1 (3)
Progressive Disease	0	6 (19)	10 (32)
Died	0	0	5 (16)‡

*One patient did not have data available at 2 months after transplantation.
†Includes 1 patient without response data available and 1 patient who is excluded after PD at 1 year (but still alive at 2 years).
‡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.

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 after transplantation (Table 2). At both 2 months and 1 year after transplantation, 65% of patients had evidence of CR or VGPR. By 2 years after transplantation, 42% of the evaluable study group was 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 the 1- and 2-year assessments. Nine of the improved response events were observed between 2 months and 1 year after transplantation, 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.

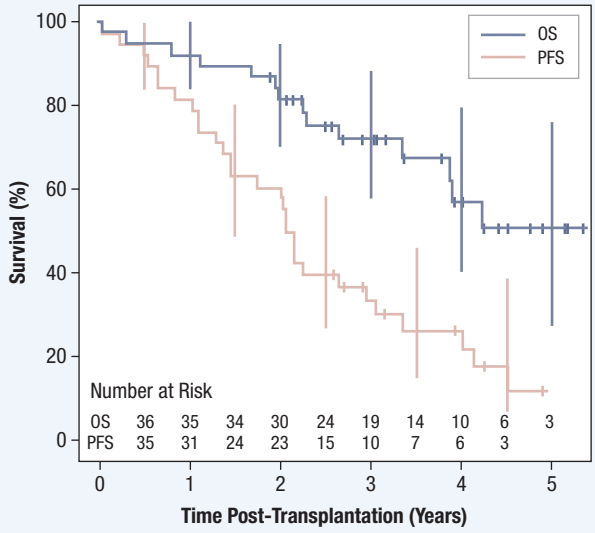
Only 1 of the 7 patients (14%) who did not receive thalidomide demonstrated an improved response, with an improvement from a VGPR to a CR between 2 months and 1 year after transplantation. Of the 7 patients who never received thalidomide, 1 patient was lost to follow-up, 1 died from sepsis

Table 3 Toxicity with Thalidomide Maintenance Therapy

Toxicity	n	Grade 1	Grade 2	Grade 3	Grade 4
Sensory Neuropathy	18*	12 (6)	5 (3)	1 (1)	0
Constipation	13	7	6 (2)	0	0
Fatigue	9	4 (1)	5 (3)†	0	0
Rash	7‡	4 (1)	2 (1)	1 (1)§	0
Infection (Without Neutropenia)	6	0	1 (1)‖	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)‖	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

Numbers in parentheses indicate events requiring dose modification.
*Four of these sensory neuropathy events led to discontinuation of thalidomide (2 grade 1 events, 1 grade 3 event, and 1 grade 4 event).
†One event of grade 2 fatigue led to discontinuation of thalidomide.
‡Three events of rash led to discontinuation of thalidomide.
§Event occurred in the setting of a patient who had experienced rash with previous thalidomide therapy.
‖One patient experiencing recurrent grade 2 sinusitis and grade 2 mucositis discontinued thalidomide.
Abbreviation: TIA = transient ischemic attack

Figure 1 Kaplan-Meier Curves for Progression-Free and Overall Survival



Kaplan-Meier plots of PFS and OS after transplantation (n = 38). Bars indicate 95% confidence intervals.

and multiorgan failure on day +11 after transplantation, and 1 patient had PD at 2 months and died during the first year after transplantation. 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 per day, with sensory neuropathy as the most common reason for thalidomide intolerance. The median tolerated dose of thalidomide was 100 mg per day. Seventeen (55%) of the 31 patients who received thalidomide successfully completed ≥ 1 year of therapy. Eleven patients continued thalidomide for > 1 year (median, 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 Common Terminology Criteria for Adverse Events version 3.0. Sensory neuropathy was the most common reason for dose modification (10 of 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 preexisting 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 pretransplantation 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 before 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 ITT 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 months). Median OS is > 5 years. At 2 and 3 years after transplantation, OS 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 after transplantation, the rates of PFS 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 MM. This therapeutic approach is associated with high response rates and prolonged durations of remission but is ultimately a noncurative therapy. Maintenance therapy after autologous transplantation 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 and its novel mechanisms of action.

The benefit of maintenance thalidomide was confirmed by the results of IFM 99-02, in which 597 patients with myeloma were randomized following tandem autologous transplantations to maintenance therapy with pamidronate alone, pamidronate plus thalidomide, or observation.[9] Thalidomide administered for 1 year after transplantation improved the response rate, and patients treated with maintenance thalidomide were observed to have a statistically significant improvement in EFS (P = .002), relapse-free survival (P = .003), and OS (P = .04).[9] In addition, a group of Tunisian investigators recently reported an improvement in 3-year OS and PFS with a 6-month course of thalidomide after a single autologous transplantation in comparison with a randomized group receiving double autologous transplantations for newly diagnosed myeloma.[10] Similarly, a large retrospective review of patients undergoing ASCT for myeloma at Emory University found that patients receiving thalidomide after transplantation had an improved median survival compared with patients who had not received thalidomide (65.5 months vs. 44.5 months) and improved OS 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 200 mg per day despite a planned targeted maintenance dose of 400 mg per day. Only 30 patients (15%) in IFM 99-02 were able to tolerate the planned dose of thalidomide 400 mg per day for a median of 12.6 months.[9] In a Canadian trial of 67 patients with myeloma randomized after transplantation to 200 mg versus 400 mg of daily thalidomide, a maintenance dose of 400 mg per day was found to be significantly more toxic, with higher rates of drug discontinuation.[14] Among patients randomized to 400 mg per day of thalidomide, 36% of patients experienced grade 3/4 toxicities, and only 41% of patients remained on thalidomide at 18 months. By comparison, 27% of patients treated with thalidomide 200 mg per day experienced grade 3/4 toxicities, and 76% of patients remained on thalidomide at 18 months.

Our data suggest that even 200 mg per day is intolerable for many patients, and 100 mg per day of thalidomide might be a more reasonable goal for maintenance therapy. The reason for the lower thalidomide dose tolerance observed in our data might 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/refractory disease at the time of transplantation (29%), lower tolerance for toxicities when thalidomide is given as maintenance therapy after autologous transplantation, 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 might be individual differences in drug metabolism leading to thalidomide intolerance (eg, sensory neuropathy), and a better understanding of the role of pharmacogenomics in thalidomide metabolism might identify patients at higher risk of AEs from thalidomide.[15] However, as these data are more representative of patient populations treated in community-based practices that constitute the majority of patients with myeloma undergoing therapy, insight can be gained into the efficacy and tolerability of thalidomide at lower dosing levels.

Maintenance therapy with lower doses of thalidomide might be an effective alternative based on previous experience with thalidomide at doses < 200 mg per day. For example, other groups have reported activity with thalidomide at doses as low as 50-100 mg per day.[10,16-18] Abdelkefi et al reported excellent tolerability of thalidomide 100 mg per day administered for 6 months after a single autologous transplantation. Rates of all grade ≥ 3 toxicities were < 5% of AEs, including peripheral neuropathy, fatigue, and constipation.[10] An Australian randomized study of single autologous transplantation followed by maintenance with thalidomide or thalidomide and alternating-day prednisolone found that 64% of patients 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 noninferiority study of high- versus low-dose thalidomide (400 mg vs. 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 per day, and thalidomide 100 mg per 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.

Conclusion

Other agents, such as the thalidomide analogue lenalidomide, are under investigation as alternative maintenance therapies after transplantation, with particular interest as to whether improved benefit or reduced toxicity can be achieved. For example, ECOG/Cancer and Leukemia Group B 100104 is a phase III placebo-controlled trial evaluating the efficacy of maintenance lenalidomide after autologous transplantation in patients with newly diagnosed myeloma.[19] In addition, recent use of a maintenance strategy with thalidomide and alternate-day prednisolone demonstrated improved 2- and 3-year PFS and OS compared with thalidomide alone following a single autologous transplantation.[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 after autologous transplantation in myeloma.

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