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Lenalidomide Maintenance for High-Risk Multiple Myeloma after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (alloHCT) with reduced-intensity conditioning is an appealing option for patients with high-risk multiple myeloma (MM). However, progression after alloHCT remains a challenge. Maintenance therapy after alloHCT may offer additional disease control and allow time for a graft-versus-myeloma effect. The primary objective of this clinical trial was to determine the tolerability and safety profile of maintenance lenalidomide (LEN) given on days 1 to 21 of 28 days cycles, with intrapatient dose escalation during 12 months/cycles after alloHCT. Thirty alloHCT recipients (median age, 54 years) with high-risk MM were enrolled at 8 centers between 2009 and 2012. The median time from alloHCT to LEN initiation was 96 days (range, 66 to 171 days). Eleven patients (37%) completed maintenance and 10 mg daily was the most commonly delivered dose (44%). Most common reasons for discontinuation were acute graft-versus-host disease (GVHD) (37%) and disease progression (37%). Cumulative incidence of grades III to IV acute GVHD from time of initiation of LEN was 17%. Outcomes at 18 months after initiation of maintenance were MM progression, 28%; transplantation-related mortality, 11%; and progression-free and overall survival, 63% and 78%, respectively. The use of LEN after alloHCT is feasible at lower doses, although it is associated with a 38% incidence of acute GVHD. Survival outcomes observed in this high-risk MM population warrant further study of this approach.

INTRODUCTION

Multiple myeloma (MM) is a heterogeneous and incurable hematologic malignancy characterized by the preferential proliferation of clonal plasma cells in the bone marrow [1-3]. Outcomes after therapy, especially progression-free survival (PFS) and overall survival (OS), vary depending on the biologic characteristics present at diagnosis, including elevated β2- microglobulin, and cytogenetic abnormalities involving

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chromosome 13 [4,5], chromosome 14 [6,7], deletion p53, hypodiploidy [8], high-risk gene expression profile, and plasmablastic morphology [9]. Patients with any of these features are considered to have high-risk MM and multiple studies have invariably shown significantly decreased PFS and OS, even in the setting of single or tandem autologous transplantation. Despite major therapeutic advances achieved in this disease, the management of patients with high-risk MM remains a challenge and an unmet need [10-12]. Current practices incorporate bortezomib-based regimens in these patients, followed by autologous transplantation (autoHCT). However, this approach fails to induce durable responses in the majority of these patients [13-15].

Although the role of alloHCT in MM remains controversial, several studies have shown encouraging PFS and OS with this treatment modality with prolonged follow-up and even in patients with high-risk disease [16,17]. In contrast to initial studies using alloHCT in MM with treatment-related mortality in the range of 40% to 50%, recent studies using nonmyeloablative and reduced-intensity conditioning regimens have shown transplantation-related mortality (TRM) rates of around 10% to 15%, with the main cause of treatment failure and mortality being disease progression [17-19]. Therefore, when considering this treatment approach in MM, post-transplantation treatment strategies need to be developed to prevent disease progression.

Lenalidomide (LEN) is an immunomodulatory drug (IMiD) with established efficacy in MM [20,21]. Although the exact anti-MM mechanism of action of LEN is unknown, a number of mechanisms are postulated to be responsible for its activity against MM, including its effect on angiogenesis, T cell proliferation, and increased cytokine production, which can lead to enhanced natural killer cell activity [22].

In the autoHCT setting, the use of LEN maintenance after transplantation was associated with prolonged PFS in 2 randomized trials and improvement in OS in 1 trial, establishing an important role for LEN as maintenance therapy [23,24].

In this study, we evaluate the tolerability, feasibility, and safety of LEN maintenance therapy after alloHCT for patients with high-risk MM.

MATERIALS AND METHODS

Patient Population

Eligible patients were 18 to 70 years of age, with chemosensitive, high-risk MM, who had received an alloHCT from an 8/8 or 7/8 HLA allele match (at A, B, C, DRB1) related or unrelated donor within 60 to 180 days of study enrollment. *High-risk MM* was defined by the presence of at least 1 of the following characteristics: deletion of chromosome 13, hypodiploidy, t(4;14), t(14;16) deletion 17p, plasmablastic morphology, elevated β2-microgolbulin (>5.5 mg/dL), or relapse after autoHCT. Patients were required to have a Karnofsky performance score ≥ 80 or Eastern Cooperative Oncology Group score ≤ 2. Patients received a reduced-intensity conditioning regimen based upon the Center for International Blood and Marrow Transplant Research (CIBMTR) definition for the alloHCT [25], and graft-versus-host disease (GVHD) prophylaxis consisted of a calcineurin inhibitor in combination with either methotrexate, mycophenolate mofetil, or sirolimus. Patients were required to have 2 separate donor recipient chimerism assessments (peripheral blood or bone marrow) before study entry. The most recent assessment needed to be ≤ 14 days before initiation of LEN. Chimerism results needed to be at least 50% donor with no evidence of falling donor chimerism when assessing both measurements.

Patients were excluded if they had active grade III to IV GVHD, absolute neutrophil count < 1500 cells/mm^3, hemoglobin level < 8.0 g/dL (transfusion support and/or erythropoietin was allowed), platelet count < 75,000 cell/mm^3 (transfusion support not allowed within the 7 days before enrollment), creatinine clearance < 50 mL/minute, total bilirubin >2 mg/dL, serum transaminases > 3 × the upper limit of normal, or had received > 3 prior lines of therapy. Lines of therapy were defined as sequential therapies separated by disease progression events.

This clinical trial was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization for Good Clinical Practice. The study was approved by the institutional review boards of all participating institutions and by the National Marrow Donor Program institutional review board. All study participants provided voluntary written informed consent.

Study Design

This was a multi-institutional, nonrandomized, open label, Phase IIa prospective trial to evaluate the safety, feasibility, and tolerability of maintenance LEN after alloHCT (CIBMTR Resource for Clinical Investigation in Blood and Marrow Transplantation Protocol 07-Rev, clinicaltrials.gov; NCT00847639). The primary objective of the study was to determine the tolerability and safety profile of a maximum of 12 cycles or 12 months from first dose (whichever came first) of LEN after alloHCT for high-risk MM. Secondary objectives were to estimate the incidences of grade III to IV adverse events, graft failure, infections, TRM, incidence and severity of acute and chronic GVHD, best response rates, and time to disease progression and OS after LEN initiation. Patients were followed from initiation of LEN maintenance therapy to 30 days after completion of 12 cycles of therapy or 12 months from first dose of study drug (whichever came first) or discontinuation of therapy.

All patients could receive supportive therapies during study participation as per institutional guidelines, including granulocyte colony–stimulating factors, erythropoietin, antiemetics, antimicrobials, analgesics, packed red blood cells, and platelet transfusions. Prophylactic anticoagulation therapy was administered at the discretion of the treating physician using aspirin, warfarin, or low-molecular-weight heparin. Treatment of GVHD was according to institutional guidelines.

Dose Escalation

Patients were treated with LEN starting within 60 to 180 days after alloHCT given on days 1 to 21 of 28 days cycles. Dose escalation and de-escalation were performed depending on tolerability to LEN. The starting dose of LEN for all patients was 10 mg/day.

If no toxicity occurred after a 28-day cycle, the dose of LEN was increased by 5 mg increments on day 1 of the subsequent cycle until the maximum dose of 25 mg/day was reached. If the patient experienced a

Table 1
Baseline Patient Characteristics

Characteristics	Value
No. of patients	30
Age, median (range), yr	54 (38-68)
Male/female	14/16 (47/53)
Disease status before LEN maintenance	
CR/VGPR/PR	15/6/9 (50,20,30)
High-risk MM Categories	
Relapse after autologous HCT	6 (20)
Beta2 microglobulin ≥ 5.5 mg/L	6 (20)
Plasmablastic morphology > 2%	5 (17)
Chromosome 13 deletion	13 (43)
t(4;14)	6 (20)
Hypodiploidy	2 (7)
17p deletion	2 (7)
t(14;16)	1 (3)
Median prior lines of therapy	1.76
Prior lenalidomide therapy	13 (43)
Unrelated/related donor	12/18
Conditioning regimens	
Fludarabine and melphalan (≤ 140 mg/m^2)	12 (40)
TBI+ fludarabine ± cyclophosphamide	8 (27)
TBI (≤ 500 cGY single/≤ 800 fractionated)	8 (27)
TBI (≤ 900 cGY fractionate) + melphalan (≤ 100 mg/m^2)	2 (7)
Time from diagnosis to AlloHCT, median (range), mo	10 (3-188)
Time from AlloHCT to maintenance, median (range), d	96 (66-171)
Follow-up, median (range), mo	21 (3-35)

CR indicates complete response; VGPR, very good partial response, PR, partial response, LEN, lenalidomide; MM, multiple myeloma; HCT, hematopoietic cell transplantation; TBI, total body irradiation; Allo HCT, allogeneic HCT.
Data presented are n (%), unless otherwise indicated.