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A Phase I Trial of High-Dose Lenalidomide and Melphalan as Conditioning for Autologous Stem Cell Transplantation in Relapsed or Refractory Multiple Myeloma

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Autologous stem cell transplantation (ASCT) conditioned with high-dose chemotherapy has long been established as the standard of care for eligible patients with newly diagnosed multiple myeloma. Despite recent therapeutic advances, high-dose melphalan (HDM) remains the chemotherapy regimen of choice in this setting. Lenalidomide (LEN) in combination with low-dose dexamethasone is recognized as a standard of care for patients with relapsed or refractory multiple myeloma (RRMM), and there is growing support for the administration of LEN as maintenance therapy post-ASCT. In view of the above, the present phase I clinical trial was designed to evaluate the safety and tolerability of high-dose LEN (HDLEN) in patients with RRMM, and to determine the maximum tolerated dose of HDLEN when added to HDM before ASCT. Despite administering HDLEN at doses of up to 350 mg/day, the maximum tolerated dose could not be determined, owing to an insufficient number of dose-limiting toxicities in the 21 patients enrolled in the trial. Conditioning with HDLEN plus HDM was associated with a favorable tolerability profile. Adverse events following ASCT were as expected with HDM. Median progression-free and overall survival were 10 months and 22 months, respectively, in this population of heavily pretreated patients. Our findings suggest that HDLEN in combination with HDM may offer significant potential as a conditioning regimen before ASCT in patients with RRMM. These preliminary findings are now being evaluated further in an ongoing phase II clinical trial.

INTRODUCTION

High-dose chemotherapy with autologous stem cell transplantation (ASCT) has been the standard of care for eligible patients with newly diagnosed multiple myeloma (MM) for almost 20 years [1-4]. ASCT allows the safe dosing of myeloablative chemotherapy, such as high-dose melphalan (HDM), which is associated with improved survival in patients with MM [4,5].

Melphalan (MEL) conditioning was first investigated more than 30 years ago, in patients with refractory malignancies, and it is still considered a preferred option when chemotherapy is used in conjunction with ASCT in patients with newly diagnosed MM [5]. In a recent randomized controlled trial (RCT) in patients with relapsed MM who had previously undergone ASCT, HDM with a second ASCT was shown to be associated with increased progression-free survival (PFS) compared with 12 weeks of oral cyclophosphamide without ASCT [6]. Despite continuing developments in MM therapy, no conditioning regimen has proven superior to the standard HDM conditioning regimen in either the upfront or the relapsed setting.

Lenalidomide (LEN) is an oral immunomodulatory drug with potent antimyeloma activity and a more favorable toxicity profile than thalidomide [7]. Based on favorable response rates and tolerability data from RCTs [8,9], combination therapy with LEN plus low-dose dexamethasone is considered a standard of care in relapsed or refractory MM (RRMM) [10]. LEN is also advocated as a maintenance therapy option following ASCT [11],

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and RCT data support the increasing use of LEN in this setting [12-14]. The antimyeloma efficacy of LEN exhibits a dose-response relationship that is limited by myelosuppression, similar to the case with MEL. In a phase I trial of LEN, the dose-limiting toxicity (DLT) of myelosuppression was evident after 28 days in almost all of the patients who received LEN 50 mg/day; consequently, 25 mg/day was established as the maximum tolerated dose (MTD) and the reference for future trials [15]. However, patients treated with LEN 50 mg/day in that trial experienced improvements in their MM, with 85% of patients responding to therapy with the single agent. Thus, high-dose LEN (HDLEN) represents a promising option for combination with HDM to augment the efficacy of ASCT by potentially overcoming resistance mechanisms seen with standard-dose LEN in RRMM, while mitigating expected secondary myelosuppression with stem cell support. Here we report a phase I trial that evaluated the safety and tolerability of HDLEN in patients with RRMM, and investigated the MTD of LEN when added to HDM before ASCT.

METHODS

Trial Design

In this single-arm clinical trial, 21 patients with RRMM received HDLEN with HDM as conditioning therapy before ASCT. The primary objective was to establish the MTD of HDLEN when added to MEL 200 mg/m^2 conditioning before ASCT in patients with RRMM. The trial protocol was approved by the Institutional Review Board of the Weill Medical College of Cornell University and New York Presbyterian Hospital, in accordance with federal regulations and the ethical principles specified in the Declaration of Helsinki. All patients provided written informed consent before enrollment. The trial was conducted at Weill Cornell Medical College between January 2010 and November 2014, and is registered at ClinicalTrials.gov (identifier NCT01054196).

Patients

Eligibility criteria included symptomatic MM with measurable disease in accordance with International Myeloma Working Group (IMWG) criteria [16]; Karnofsky performance status ≥70 (or ≥60 if the decrease in Karnofsky performance status was due to lytic bone disease); disease progression after at least 1 previous line of therapy (which may have included LEN or ASCT); the ability to receive low-molecular-weight heparin anticoagulation; adequate organ function, with creatinine clearance ≥60 mL/min, total bilirubin ≤1.5 times the upper limit of normal and transaminases ≤2.5 times the upper limit of normal; adequate CD34$^+$ stem cell reserves to support transplantation (≥2 × 10^6/kg CD34$^+$ cells); and disease classified as refractory according to IMWG criteria (MM progression on or within 60 days of last therapy) [17].

Conditioning Therapy

MEL was infused at a dose of 200 mg/m^2 (MEL200) split over days –2 and –1 before ASCT (patients received ASCT on day 0; Figure 1). On the day of MEL infusion, each patient was offered oral cryotherapy with ice chips for 6 hours [18]. Oral HDLEN was administered on days –5 to –1. The HDLEN dose was escalated according to a modified Fibonacci schedule in a 3 + 3 design until the onset of DLT. DLT was defined as grade 3 mucositis, diarrhea, nausea, vomiting, or febrile neutropenia that did not resolve to grade ≤2 by day +21; any other nonhematologic adverse event (AE) that did not resolve to grade ≤2 within 72 hours (with the exception of alopecia); or any occurrence of a grade 4 nonhematologic AE. Failure to engraft, absolute neutrophil count ≥500/mL by day +24, and platelet count ≥20,000/μL without transfusion support by day +42, were each considered a DLT.

Six HDLEN cohorts, as defined in Figure 1, were investigated: (1) 25 mg twice daily, (2) 25 mg in the morning (AM) and 50 mg in the evening (PM), (3) 50 mg AM and 75 mg PM, (4) 75 mg AM and 100 mg PM, (5) 100 mg AM and 150 mg PM, and (6) 150 mg AM and 200 mg PM. Three subjects were enrolled to each cohort; if a DLT was encountered at a particular dose level, then the cohort at this dose level was expanded to 6 patients. If 2 DLTs occurred at the same dose level, then the previous dose level was defined as the MTD. All patients received prophylactic anticoagulation with low molecular weight heparin 40 mg/day, administered subcutaneously on days –5 to +14; this treatment was withheld when the platelet count dropped to <50,000/μL.

ASCT and Maintenance Therapy

Stem cell infusion of at least 2 × 10^6 CD34$^+$ cells/kg was performed 24 to 72 hours after the final MEL dose. Subsequently, starting on day +1, patients received granulocyte colony-stimulating factor with standard supportive care until engraftment, defined as an absolute neutrophil count > 500/μL for 48 hours. Platelet engraftment was defined as a platelet count ≥ 20,000/μL without transfusion support. Patients received levofloxacin, acyclovir, and fluconazole antimicrobial prophylaxis starting on day +1, red blood cell and platelet transfusions as needed, and other supportive care on an inpatient basis from the first dose of chemotherapy until engraftment. For maintenance therapy, all patients received LEN 25 mg/day for days 1 to 21 of a

Treatment phase

Day	–5	–4	–3	–2	–1	24–72 hours after last melphalan dose
	Lenalidomide					Day 0
				Melphalan 100 mg/m^2	Melphalan 100 mg/m^2	Stem cell infusion

Lenalidomide dose escalation

Cohort	Lenalidomide dose / schedule	No of days
1	25 mg twice daily	5
2	25 mg every morning, 50 mg every evening	5
3	50 mg every morning, 75 mg every evening	5
4	75 mg every morning, 100 mg every evening	5
5	100 mg every morning, 150 mg every evening	5
6	150 mg every morning, 200 mg every evening	5

Maintenance phase

Starting day +100 (post-stem cell infusion)
Lenalidomide 25 mg daily on days 1–21 of a 28-day cycle until progression of disease
Aspirin 81 mg daily continuously throughout the maintenance phase

Figure 1. Pre-ASCT conditioning regimen and post-ASCT maintenance therapy.