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High-Dose Topotecan, Melphalan and Cyclophosphamide (TMC) with Stem Cell Support: a New Regimen for the Treatment of Multiple Myeloma

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The goal of this trial was to assess the toxicity and potential efficacy of high-dose topotecan, melphalan and cyclophosphamide as a preparative regimen for patients with multiple myeloma undergoing autologous stem cell transplantation. Eighteen patients were treated, 8 for first remission consolidation, 4 with relapse sensitive disease, 3 primary refractory and 3 relapsed refractory. The median age was 56 (38–65) and the median number of prior regimens was 3 (1–8). Patients received cyclophosphamide 1 g/m^2/d on days −6, −5, −4; melphalan 70 mg/m^2 on days −3, −2 and topotecan 3.0 to 3.5 mg/m^2/d on days −6 to −2. Peripheral blood stem cells were infused on day 0. Toxicity (Bearman Toxicity Criteria) was mostly limited to grade 1–2 mucositis and grade 1 diarrhea. There were no transplant-related deaths. The overall response rate at 3 months post transplantation was 89% with 17% CR, 2 of those in refractory patients. The overall response rate in refractory patients was 67%. With a median follow up of 12.3 months, 89% of patients are alive. The TMC regimen is well tolerated and produces high response rates. Further evaluation of TMC to fully assess response and survival is ongoing.

Keywords: Topotecan; Melphalan; Cyclophosphamide; Transplantation; Multiple myeloma

INTRODUCTION

The combination of melphalan and prednisone has been the standard of care for the treatment of multiple myeloma for the past 25 years. Strictly defined complete remissions are rare with this approach, usually less than 5%, and the median survival is approximately 3 years [1]. The randomized trial of high-dose vs. standard chemotherapy by Attal *et al.* [2], showed a survival advantage for the transplant arm; since then, dose intensification with stem cell support has become one of the most widely used strategies for the treatment of multiple myeloma [3–5]. Despite definite improvement in supportive care over the past few years, transplant-related morbidity and mortality remains a concern. In an attempt to reduce toxicity without compromising efficacy, a new drug combination was explored. In this study, the experience with the combination of high-dose topotecan, melphalan and cyclophosphamide (TMC) in patients with multiple myeloma, is reported. The goals were to assess the toxicity of this high-dose regimen and to determine if TMC has activity in patients with multiple myeloma.

PATIENTS AND METHODS

Between September 1999 and May 2000, 18 patients with multiple myeloma received high-dose chemotherapy with autologous peripheral blood stem cell transplantation as part of a pilot trial of a new preparative regimen for this diagnosis. Patients provided written informed consent and were enrolled on a protocol approved by the institution's internal review board. Patient's demo-

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graphics and disease characteristics are summarized in Table I.

Eligibility Criteria

Patients were eligible for this study if they had a diagnosis of intermediate or high tumor mass multiple myeloma. Patients in first or greater than first remission (complete or partial), primary refractory disease, and refractory relapsed disease were eligible. Patients had to be between the physiological ages of 15 to 65 years, have a Zubrod performance status less than 3 and a life expectancy of at least 12 weeks. Other eligibility criteria included: left ventricular ejection fraction $\geqslant 50\%$; pulmonary diffusion capacity $\geqslant 50\%$; serum creatinine < 1.5 mg/dl; serum bilirubin less than twice the upper limit of normal; no evidence of chronic or active hepatitis or cirrhosis; no active central nervous system disease; platelet count greater than 100×10^9/l.

TREATMENT PLAN

Blood Stem Cell Mobilization and Collection

For peripheral blood stem cell mobilization and collection, patients received either filgrastim alone or standard chemotherapy followed by filgrastim. A minimum of 3×10^6 CD34+ cells/kg was required to proceed with the high-dose treatment. The optimal targeted dose was $\geqslant 4 \times 10^6$ CD34+ cells/kg. Apheresis was performed using the COBE Spectra Version 4.7 cell separator (COBE BCT, Lakewood, CO, USA). The CD34+ cell content of the collection product was measured immediately after apheresis. The cells were subsequently cryopreserved using programmed freezing.

TABLE I Patient Demographics

$n = 18$
M/F: 12/6
Median Age: 56 (range 38–65)
Monoclonal Immunoglobulin:
IgG: 11 patients
IgA: 4
Light chain only: 2
Non-secretory: 1
Disease status prior to transplantation
First remission: 8 patients (8 PR, 0 CR)
Relapse sensitive: 4 (4 PR, 0 CR)
Primary refractory: 3 (2 MR, 1 SD)
Relapse refractory: 3 (2 SD, 1 PD)
Median marrow plasma cell content: 3.5% (range 0–64%)
Median serum paraprotein level: 0.85 g/100 ml (0–4.6)
Median number of prior chemotherapy regimens: 3 (1–8)
Median β_2 microglobulin prior to transplant: 3.2 mg/l (1.3–20.3)
Median time from diagnosis to transplant: 12 months (4–172)

High-Dose Chemotherapy Regimen

The high-dose chemotherapy regimen consisted of topotecan, melphalan, and cyclophosphamide. Cyclophosphamide 1 g/m^2/d was given intravenously over 2 h on days -6, -5, -4; melphalan 70 mg/m^2/d was given intravenously over 30 min on days -3 and -2. Both these agents were administered immediately before the topotecan. Topotecan was given intravenously at a starting dose of 3 mg/m^2/d over 30 min for 5 total doses on days -6 to -2. This topotecan dose was well tolerated and after 4 patients, the dose was increased to 3.5 mg/m^2/d $\times$ 5 days for the remaining 14 patients. For patients greater than 20% above ideal body weight, all chemotherapy agents were dosed based on adjusted body surface area. To minimize oral mucositis, patients were instructed to keep ice chips in their mouths starting 5 min before, during, and for 1 h following the melphalan and topotecan infusions.

Supportive Care

Continuous intravenous fluid hydration was administered from day -7 until blood count recovery. Filgrastim at 5 mg/kg rounded to the nearest vial size was given subcutaneously daily from day 0 until the absolute neutrophil count reached at least 1.5×10^9/l. Prophylactic antibiotics with levofloxacin (500 mg orally daily), fluconazole (200 mg orally daily) and valacyclovir (500 mg orally daily) were administered. Transfusions of blood products were administered to maintain a hemoglobin level above 8.0 g/dl and platelets above 15×10^9/l.

Criteria for Response

Response to the transplant regimen was assessed by the criteria developed by the EBMT/ABMTR/IBMTR [6]. Complete response (CR) was defined as the absence of monoclonal protein in serum and urine by both immunoelectropheresis and immunofixation, a normal bone marrow and no increase in size or number of bone lesions. Partial response (PR) was defined as a reduction of more than 50% in the level of serum monoclonal protein or greater than 90% of urinary light chain excretion (or to less than 200 mg per day). All responses had to be maintained for at least 6 weeks. For patients with non-secretory disease, responses were evaluated by serial bone marrow aspirations. CR required less than 5% plasma cells in the marrow and PR required a 50% reduction in marrow plasmacytosis. No response was defined when the above criteria were not fulfilled. Relapse or progression required a 25% increase in the level of paraprotein on two consecutive tests or reappearance of a paraprotein after CR. For assessment of response, post-transplant paraprotein levels were compared to immediate pre-transplant level. When transplantation was performed as consolidation of prior response, post-

transplant paraprotein levels were compared to the level prior to the start of initial chemotherapy. The post-transplant response in patients with chemosensitive disease was by definition at least a PR, unless they progressed or died within 6 weeks. Patients were evaluated for response at 1 month and 3 months post transplantation.

Statistical Analysis

All analysis were performed using Statistica for Windows Release 5.1 (StatSoft, Tulsa, OK, USA).

RESULTS

Patients

A total of 18 patients were treated. The median number of prior chemotherapy regimens was 3 (range 1–8). The median age was 56 years (range 38–65). All patients were assessed for regimen-related toxicity and response at 3 months post transplantation. Since this was a pilot trial, post-transplant maintenance therapy was allowed after 3 months. Ten patients received thalidomide with dexamethasone, 1 patient received dexamethasone alone and 1 received thalidomide alone for maintenance therapy.

Toxicity

There were no transplant-related deaths. Toxicity to the preparative regimen was evaluated using the Bearman Toxicity Criteria [7] and is described in Table II. Grade 1–2 mucositis and grade 1 diarrhea were the most commonly observed toxicity. Mucositis was the major toxicity, grade 2 observed in 56% of all patients. Postural hypotension was observed in patients not receiving at least 2 liters/day of intravenous hydration. There was no grade 3 or 4 toxicity, but concerned that further dose escalation of topotecan would lead to such toxicity, no patient received more than 17.5 mg/m^2 (total dose) of topotecan. One patient developed grade 2 hemorrhagic cystitis which was self limiting. Urine cytology was suggestive of viral cytopathic effect. The median time to recovery of an absolute neutrophil count $> 0.5 \times 10^9$/l was 9 days (range 8–10). The median time to platelet recovery $> 50 \times 10^9$/l was 14 days (range 8–31).

Tumor Response

Response was assessed at 1 month and 3 months post transplantation and is summarized in Table III. Response was documented in 89% of patients (16/18). Three patients (17%) achieved a CR. The response rate among the chemo-refractory patients was 67% (4/6) with 2 patients achieving a CR. One complete remission was in a patient with relapsed refractory plasma cell leukemia. After initiation of maintenance therapy, 2 patients out of the 16 responders achieved a CR, for a cumulative CR rate of 28%. With a median follow up of 12.3 months, 89% of patients are alive and 72% of patients are progression-free.

DISCUSSION

High-dose chemotherapy is an effective treatment for patients with multiple myeloma. Melphalan has been the most extensively used agent for intensification; in the mid 1980's [8] early results suggested a high response rate in patients with refractory disease given high doses of melphalan. Barlogie *et al*. [9] demonstrated that high-dose melphalan could be safely given with reduced myelotoxicity with the use of bone marrow progenitor cells. Attal *et al*. [2] randomized 200 previously untreated patients with multiple myeloma to receive either conventional chemotherapy or high-dose chemotherapy with autologous bone marrow transplantation. The response rate among the patients who received high-dose therapy was 81%, and 57% in the standard dose group. This translated into a higher probability of a 5-year event-free survival and overall survival for the high-dose group compared to the conventional dose group. The preparative regimen used was melphalan and total body irradiation.

Recent studies have also explored the concept of tandem autologous transplantation. The University of Arkansas reported on patients receiving two melphalan based high-dose treatments [10]. When comparing with case-matched controls, the tandem approach had a superior response rate, median EFS and OS. With the underlying theory that increasing the CR rate can lead to improved survival, randomized studies of single vs. tandem transplants have been conducted with mixed results. Although the improved CR rate was associated with an improved OS and EFS in the Spanish study of Lahuerta *et al*. [11], these results could not be duplicated

TABLE II Toxicity

Total Topotecan Dose	Mucositis no patients (%)		Diarrhea no patients (%)	
	Grade 1	Grade 2	Grade 1	Grade 2
15 mg/m^2	1/4 (25%)	3/4 (75%)	3/4 (75%)	0/4 (0%)
17.5 mg/m^2	3/14 (21%)	7/14 (50%)	7/14 (50%)	0/14 (0%)

TABLE III Response at 3 months post transplantation

Response rate (CR + PR): 89% (16/18)
Stable disease: 5% (1/18)
Progressive disease: 5% (1/18)
CR rate: 17% (3/18)
Response in chemorefractory pts: 67% (4/6)
2 CR and 2 PR

by the Dutch-Belgian Hemato-Oncology Cooperative Study Group (HOVON) [12]. In this latter study, a second myeloablative transplant with cyclophosphamide and total body irradiation increased the CR rate and time to progression but had no impact on survival. The overall poor prognostic factors of the study group and the preparative regimens are possible explanations for these findings. Cyclophosphamide and TBI may be inferior to high-dose melphalan, and this combination has been largely abandoned as preparative regimen. The potential benefit of an increased CR rate may be most significant for patients with favorable prognostic factors, and exploring treatments with the potential of increasing the CR rate could still be important for this subgroup of patients.

Since then, studies have compared different melphalan-based regimens [13–14] and have failed to show an improvement in survival for the TBI containing combinations, leaving melphalan 140–200 mg/m^2 as the most widely used preparative regimen for autologous transplantation. The combination of high-dose topotecan with melphalan and cyclophosphamide had been previously studied in a group of 53 patients with advanced ovarian cancer. None of the 53 patients treated had died from regimen-related complications and toxicity was mostly limited to mucositis [15]. Topotecan is a semisynthetic analog of the alkaloid camptothecin and is one of the several new cancer drugs derived from this compound. Similar to the parent compound, topotecan acts specifically to interfere with the nuclear enzyme topoisomerase I. Topotecan has shown activity in multiple myeloma. Kraut *et al*. [16] treated 43 patients with relapsing or resistant multiple myeloma. Topotecan was administered at a dose of 1.25 mg/m^2 daily for 5 days as a single agent. The objective response rate was 16% with a median survival of 28 months. Myelosuppression is topotecan's major toxicity [17], but in the context of transplantation this is not dose limiting. Cyclophosphamide is also active against multiple myeloma and has shown synergistic effects when used in combination with topotecan [18–19]. This constitutes the basis for our study of the TMC regimen in patients with multiple myeloma. In this study we have demonstrated that the combination of high-dose topotecan, melphalan and cyclophosphamide can be administered safely and with acceptable toxicity in patients with multiple myeloma. None of the 18 patients treated died from regimen-related complications. Toxicity seemed to be mostly limited to diarrhea and mucositis. At the 17.5 mg/m^2 dose of topotecan 71% of the patients experienced grade 1 or 2 mucositis.

One goal is to develop a high-dose regimen which can lead to a high CR rate while minimizing toxicity. The toxicity profile of the TMC drug combination has allowed delivery of very high doses of these agents without regimen-related mortality. It is important to note however, that although the combination is well tolerated, the chemotherapy is administered over 5 days and it remains mostly an inpatient regimen. Many of the current high-dose regimens for multiple myeloma are given safely in the outpatient setting. Overall, 89% of the patients responded with 17% achieving a stringently defined CR. Two out of 6 patients with chemo-refractory disease meet the criteria for CR post transplantation. After initiation of maintenance therapy, 2 additional patients achieved a CR, for a total CR rate of 28%. The TMC regimen is well tolerated, leads to a high response rate and has not produced toxicity beyond the treatment duration. We are currently evaluating this regimen further as a single transplant, and as a second transplant in a tandem approach to assess its impact on response rate and survival.

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