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Clinical Research

Safety and Cost-Effectiveness of Outpatient Autologous Stem Cell Transplantation in Patients with Multiple Myeloma

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A B S T R A C T

High-dose chemotherapy with autologous stem cell transplantation (ASCT) remains the standard of care for patients with multiple myeloma. Outpatient ASCT can be an attractive option given wait times and costs associated with inpatient procedures. We initiated an outpatient transplantation protocol in 2006. Patients were treated at a university hospital outpatient clinic that was open 5 days a week. The present study investigated safety and cost-effectiveness of the outpatient program. Ninety-one patients underwent ASCT between 2006 and 2010. The majority of patients (77%) had Durie-Salmon stage III disease; 38% had 1 or more comorbidities. Seventy-six patients (84%) were hospitalized during the first 100 days, mainly for febrile neutropenia (n = 71). Overall survival at day 100 was 100%. No patient was admitted to an intensive care unit. Risk factors for prolonged hospitalization (longer than 7 days) were disease stage IIB or higher and age >60 years. The cost savings was $19,522 (Canadian dollars) per patient compared with inpatient ASCT, for an annual savings of approximately $740,000. In summary, outpatient ASCT performed in a weekday clinic for patients with multiple myeloma appears to be safe and cost-effective, but is associated with a relatively high hospitalization rate.

INTRODUCTION

High-dose chemotherapy with autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM) was first reported in 1986 [1]. Although ASCT does not result in a cure, it is associated with better disease-free survival and overall survival compared with treatment with conventional chemotherapy alone [2]. This strategy remains the standard of care in younger patients, even with the introduction of new therapeutic agents.

Traditionally, ASCT for patients with MM and other hematopoietic malignancies has been performed in the inpatient setting because of the myeloablative nature of the preparative regimen and concerns for patient safety. With better understanding of the disease and improvements in supportive care, initial trials of ASCT in the outpatient setting were conducted [3-5]. Outpatient ASCT requires the institution of an interdisciplinary team comprising physicians, nurses, pharmacologists, nutritionists, and social workers [6]. The outpatient approach has become particularly attractive given that many transplantation centers face chronic bed shortages and financial constraints [7,8]. In addition, MM is considered the most frequent indication for ASCT in North America and Europe, resulting in considerable strains on hospital bed availability [9].

The aims of the present study were to analyze the safety of ASCT in a homogenous cohort of 91 consecutive patients with MM performed in the outpatient setting at our institution, and to evaluate possible cost-effectiveness of the procedure compared with traditional inpatient ASCT.

PATIENTS AND METHODS

Patients

This study is a retrospective review of 91 consecutive adult patients with MM who underwent outpatient ASCT at our hospital. All patients were treated on a uniform treatment protocol. Transplantations were performed between January 2006 and December 2010. Patient outcomes were recorded during the first 100 days posttransplantation. The study was approved by our hospital's Institutional Review Board, and all patients signed informed consents, which allowed data collection and analysis.

Patients were diagnosed with MM and considered eligible for ASCT according to accepted institutional criteria and guidelines. Most patients were referred from other centers and received induction chemotherapy at the discretion of their treating physician. The majority of patients received vincristine-adriamycine-dexamethasone (VAD)-based chemotherapy. Patients with either chemotherapy-sensitive disease (with complete response [CR], very good partial response [VGPR], or partial response [PR]), as well as those with stable disease (SD) or progressive disease (PD), were eligible for ASCT.

The pretransplantation workup involved assessment of disease status; screening for infectious diseases; assessment of cardiac, pulmonary, and renal function by electrocardiography; multiple gated acquisition scan, complete pulmonary function studies, and 24-hour urine collection for creatinine clearance; and screening for other comorbidities as indicated. Disease status was determined based on the international uniform response criteria from the International Myeloma Working Group guidelines [10]. Psychiatrists and/or social workers evaluated patients as required. Only patients with a left ventricular ejection fraction >40% and a corrected lung CO diffusion capacity of ≥50% were eligible for ASCT. Outpatient transplantation was offered to patients on a voluntary basis. All patients age <66 years were eligible. Patients age 66-69 years were considered if in good health. Other requirements were the absence of significant comorbidities as determined by the treating physician, the availability of a caregiver, and residence close to our center (within a 45-minute drive) or acceptance to stay at an accommodation close to the hospital. Two lodging facilities, which are located close to our hospital and run by privately funded volunteer

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organizations independent of our institution, offered patients and their caregivers accommodation and meals for a nominal charge. These charges were covered at no cost to the patient or caregiver either directly or after application for reimbursement by the patient's referring institution, or by the provincial healthcare plan.

Caregivers were adult members of the patient's family or close friends. They provided direct assistance to the patient and accompanied the patient to our outpatient clinic.

Stem Cell Mobilization

Stem cell mobilization was performed using cyclophosphamide 1.5 g/m^2 i.v. and granulocyte colony-stimulating factor (G-CSF) 5 μg/kg s.c. every 12 hours [11,12]. Grafts were collected by large-volume apheresis using a COBE Spectra apheresis system (Caridian BCT, Mississauga, Ontario, Canada) as soon as the peripheral blood CD34$^+$ cell count exceeded 10/μL. A minimum of 8 × 10^6 CD34+ cells/kg were collected, allowing for the possibility of a second transplantation if required. Grafts were frozen using DMSO 10% in at least 2 bags and kept in storage at a temperature below −150°C in the vapor phase of nitrogen, as described previously [13].

ASCT Procedure

All patients were assessed and followed at a dedicated outpatient unit, in close proximity to the hospital's emergency room and inpatient and laboratory facilities. No protective isolation besides gloves and a nonsterile mask were used. The unit was open during weekdays. All treatments and follow-up assessments were performed in this unit. Medications were administered via a central venous catheter inserted into the subclavian vein (a Broviac line in most cases) [14]. The catheter was inserted on day -3 under local anesthesia by an experienced radiologist. On day -2, the patient received high-dose chemotherapy with melphalan (all but 3 patients at a dose of 200 mg/m^2, with 2 receiving 100 mg/m2 and 1 receiving 140/m^2). On day 0, the graft was thawed at the patient's bedside and infused in the outpatient unit. A minimum graft of 2 × 10^6 CD34+ cells/kg was required. Patients were followed daily from day -3 to day 0 and consecutively 3 times weekly thereafter, or more often if required.

Antimicrobiologic Prophylaxis and Treatment

Patients received ciprofloxacin 500 mg twice daily from day 0 until neutrophil engraftment or the initiation of i.v. antibiotics for neutropenic fever (mainly ceftazidime). For patients seropositive for herpes simplex virus, prophylaxis with valacyclovir 500 mg daily from day -2 until neutrophil engraftment was instituted. Patients seropositive for varicella zoster virus received valacyclovir 500 mg twice daily for up to 3 months posttransplantation or longer at the discretion of the treating physician. Antifungal prophylaxis with fluconazole 400 mg/day was started at day 0 and continued until neutrophil engraftment. *Pneumocystis jiroveci* prophylaxis with trimethoprim/sulfamethoxazole, 1 double-strength tablet thrice weekly or twice daily on weekend days, was started after engraftment and continued for 3 months posttransplantation. In the event of intolerance or allergy to trimethoprim/sulfamethoxazole, atovaquone or inhaled pentamidine was used in some patients.

Other Supportive Measures

G-CSF 5 μg/kg was started in all patients on day +7 and continued until neutrophil engraftment. G-CSF was either self-administered or given by a caregiver or a home care nurse. Packed RBCs were used to maintain a hemoglobin level >80 g/L, and 5 units of platelets were transfused to maintain a count <15 × 10^9/L. All blood products were leukocyte-depleted, irradiated, and cytomegalovirus (CMV)-negative (in CMV-negative patients). Patients received i.v. hydration and electrolyte support in accordance with institutional guidelines.

Hospital Admission

Criteria for admission were uncontrolled nausea and/or vomiting, inability to eat or swallow tablets related to mucositis, insufficient pain control, significant diarrhea or abdominal cramps, febrile neutropenia, or judgment of the transplantation physician based on the patient's clinical course and performance status.

Engraftment

Neutrophil engraftment after ASCT was defined as the first of 3 consecutive days of an absolute neutrophil count exceeding 0.5 × 10^9/L. Platelet recovery was defined as the first of 3 days with a blood platelet count exceeding 20 × 10^9/L without transfusion support for 7 consecutive days.

Statistical and Cost Analyses

Clinical data were obtained from a prospectively collected electronic database and by retrospective chart review. A predefined set of data was collected. Continuous variables were summarized using mean ± standard deviation and median (range) values; categorical variables are presented as frequencies and percentages. Associations between hospitalization and other characteristics were tested using Pearson's χ^2 test and Mood's median test. The description of follow-up hospitalization was done using 95% confidence intervals. All analysis were done using SPSS version 15 (IBM, Armonk, NY), with significance set at $P < .05$. Based on information provided by our institution for the year 2006 and using the mean number of hospitalization days, the mean cost of transplantation was computed separately for both inpatient and outpatient ASCT groups. Charges were calculated and reported in Canadian dollars (C$).

RESULTS

Patient Characteristics

Between 2006 and 2010, 180 patients underwent ASCT for MM at Maisonneuve Rosemont Hospital. Ten of these patients underwent 2 transplantations, resulting in a total of 190 transplant procedures. Ninety-one patients (51%) underwent ASCT in an outpatient setting and were included in our analysis. Fifty-three of these patients (58%) were male, and the median age at diagnosis was 56 years (range, 34-66 years). Approximately one-half of the patients had IgG myeloma (49%) and stage III disease according to the Durie-Salmon classification scheme [15]. Two patients had stage I myeloma with progressive disease, requiring therapy. International Staging System parameters were available for only 48 patients (53%). Creatinine level at diagnosis was <177 μmol/L in 76 patients and ≥177 μmol/L in 15 patients. The majority of patients had creatinine and lactate dehydrogenase values within normal ranges before undergoing ASCT (day -2). Patient characteristics are summarized in Table 1. The median Eastern Cooperative Oncology Group performance status [16] at transplantation was 0 (range, 0-2). Thirty-five patients (38%) had comorbidities: 17 with 1 comorbidity, 11 with 2 comorbidities, and 7 with 3 comorbidities.

Induction Chemotherapy

The patients underwent a median of 1 course of therapy (range, 1-3) before ASCT. We identified 15 different schedules and combinations. In the majority of cases (59%), VAD or VAD followed by other schedules was used. Eighteen patients (20%) experienced 10 different complications during induction therapy, including infectious (n = 9), thromboembolic (n = 4), neuropsychiatric (n = 4), and gastrointestinal (n = 1) problems. Twenty-six patients (29%) underwent local radiotherapy before stem cell mobilization. Forty-two patients (46%) were treated with bisphosphonates after the diagnosis of MM.

Response Status at ASCT

The response to induction therapy was evaluated before stem cell mobilization. Four patients (4%) achieved a stringent CR (sCR), 6 patients (7%) achieved a CR, 8 patients (9%) achieved a VGPR, and 61 patients (67%) achieved a PR. Eleven patients proceeded to ASCT without achieving at least a PR. Nine patients (10%) had SD, and 2 (2%) had PD.

Stem Cell Mobilization and Collection

Stem cell mobilization was performed as described above. Two patients (2%) required a second mobilization attempt. These patients were remobilized with the same regimen used previously, with the addition of ancestim (Stemgen; Amgen, Mississauga, Ontario, Canada) at a dose of 20 μg/kg. The median number of aphereses was 1 (range, 1-6), and median CD34$^+$ cell collection was 12.5 × 10^6/kg (range, 5-47.5 × 10^6/kg).