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Long-Term Outcome of Myeloablative Allogeneic Stem Cell Transplantation for Multiple Myeloma

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ABSTRACT

Allogeneic stem cell transplantation (alloSCT) has been used in the hopes of harnessing the curative potential of the graft-versus-myeloma effect. This study examines the long-term outcomes of a large cohort of patients with myeloma who were treated with myeloablative alloSCT at a single center. Comparisons are made with those who were treated with autologous stem cell transplantation (ASCT). Between January 1989 and February 2002, 158 patients age ≤55 years underwent SCT for myeloma. Seventy-two patients underwent myeloablative alloSCT (58 related; 14 unrelated), whereas 86 patients underwent ASCT. Most patients received single-agent high dose dexamethasone or VAD (vincristine, adriamycin, dexamethasone) therapy pre-SCT. Conditioning regimens were melphalan-based for all ASCT patients, whereas the alloSCT patients received melphalan-based (70%), total-body irradiation (TBI)-based (18%), or other (13%). Patients who underwent alloSCT were younger, had a higher Durie-Salmon stage disease, and a shorter median time from diagnosis to transplant. Myeloma subtypes were similar between groups. Other pre-SCT (BMT) characteristics were similar except that ASCT patients had a higher proportion of cases that received palliative radiotherapy pre-SCT. Disease response pre-SCT was similar. At last follow-up, 61 of 158 patients are alive with a median follow-up of 88.4 months (range: 35.5-208.5). The overall survival (OS) of the alloSCT cohort was 48.1% at 5 years and 39.9% at 10 years compared to 46.2% at 5 years and 30.8% at 10 years for the ASCT cohort ($P = .94$). The event-free survival of the alloSCT cohort was 33.3% at 5 years and 31.4% at 10 years compared to 32.9% and 15.2%for the ASCT cohort ($P = .64$). Treatment-related mortality (TRM) at 1 year was 22% for the alloSCT cohort and 14% in the ASCT cohort ($P = .21$). Cumulative incidence of grade II-IV acute graft-versus-host disease (aGVHD) was 72% and the cumulative incidence of chronic GVHD (cGVHD) was 68% at 2 years. Neither aGVHD nor cGVHD had an influence on OS or event-free survival, although 5 of 14 patients who have received donor lymphocyte infusions (DLI) have had disease response. The risk of relapse was reduced in those who developed aGVHD ($P = .02$) but not cGVHD ($P = .23$). In conclusion, although there are patient who are alive without disease >10 years post myeloablative alloSCT, similarly there are long-term survivors post-ASCT. Myeloablative alloSCT should not be considered standard treatment, and should only be considered in the context of a clinical trial.

KEY WORDS

Multiple myeloma • Allogeneic stem cell transplantation • Graft-versus-myeloma

INTRODUCTION

Autologous stem cell transplantation (ASCT) is routinely offered to eligible patients with multiple myeloma. Although the survival benefit of ASCT compared to conventional chemotherapy is in dispute, the relatively low morbidity and mortality rate make it an attractive therapeutic modality [1-5]. Unfortunately, for most patients, their myeloma eventually relapse requiring further therapy.

Allogeneic stem cell transplantation (alloSCT) has been utilized in the hopes of lowering relapse rates and increasing survival. Possible reasons for the lower risk of relapse is the use of stem cells uncontaminated by tumor cells and more importantly the graft-versus-myeloma (GVM) effect [6,7]. Previous reports describing the experience of fully myeloablative alloSCT have limited median follow-up of survivors of <5 years [8-12]. Because of the chronic nature of myeloma, longer follow-up would be informative. Most of these reports conclude that alloSCT results in reduced risk of relapse, which is countered by increased treatment-related mortality (TRM). The European Bone Marrow Transplantation (EBMT) Registry has performed a retrospective analysis showing the overall survival (OS) of patients who underwent myeloablative alloSCT was inferior to case-matched patients who underwent ASCT [13]. Similar to the other reports, the poor outcome of patients receiving alloSCT was attributed to a higher TRM but the rate of relapse was not reduced when compared to ASCT.

SCT has been offered to patients with multiple myeloma in Vancouver since 1989. A previous publication described our initial results [14]. This report describes our updated results with increased number of patients and an extended median follow-up of surviving patients of >8 years. Patients who received alloSCT were compared to those who received ASCT with respect to OS and event-free survival (EFS). Direct comparison is not possible because of the retrospective nature of this study and problems with selection bias, but was performed to help assess and illustrate the limitations of myeloablative alloSCT.

PATIENTS AND METHODS

Patients and Study Design

Approval from the University of British Columbia (UBC) research ethics board was obtained to retrospectively review patient data for this study. Patients were eligible for alloSCT up to age 55. Patients were eligible for ASCT up to age 65, but only those up to the age of 55 were included in this study to allow for a more appropriate comparison with patients who received an alloSCT. Between February 1989 and February 2002, 232 patients underwent SCT for multiple myeloma of whom 159 were <56 years of age at the time of transplantation. Informed consent was obtained before proceeding to transplant. Charts and records from a computerized database of all patients were reviewed. Seventy-two alloSCT recipients (58 related donor and 14 unrelated donor) and 86 ASCT recipients were included for analysis. One patient who received a syngeneic transplant was excluded. One patient who had received an ASCT at another center received an alloSCT for relapsed disease at our institution. This patient is included in the alloSCT group. No other patient received >1 transplants. All patients had adequate cardiac, pulmonary, hepatic, and renal function based upon predefined criteria. Patients had to have a serum creatinine of ≤200 μmol/L and at least stable disease following induction therapy to be eligible for ASCT. Patients with progressive disease remained eligible for alloSCT. No formal criteria were used in determining which patients should be offered alloSCT instead of ASCT. All patients were discussed within the physician group. In general, patients with younger age, more advanced or less responsive disease, were offered alloSCT if they were deemed fit to survive the procedure. Baseline patient characteristics are presented in Table 1.

Induction Therapy, Conditioning Regimens, and Stem Cell Source

Pretransplantation therapy varied based on the time period during which the patient was initially assessed for transplantation. Patients may have received melphalan-based chemotherapy prior to referral to our center, although it was our recommendation that this be avoided. Induction therapy typically consisted of vincristine, doxorubicin, dexamethasone (VAD)-based [15] chemotherapy or single-agent dexamethasone followed by peripheral blood stem cell collection (PBSC) or bone marrow harvest. Early patients were more heavily pretreated and received up to 4 regimens pretransplant. The strategy of utilizing single-agent dexamethasone with minimal delay before proceeding to transplantation was eventually adopted to minimize potential toxicity prior to intensive therapy. All but 3 patients received high-dose dexamethasone alone or in combination with VAD prior to SCT . Radiation therapy was used for patients with plasmacytomas, pathologic fractures, or for palliative symptom relief prior to SCT.

The conditioning regimen for both ASCT and related donor alloSCT typically consisted of oral busulfan (12 mg/kg), intravenous (i.v.) melphalan (100 mg/m^2) and cyclophosphamide (90 mg/kg). Patients undergoing volunteer unrelated donor transplantation received total-body irradiation (TBI) 1200 cGy given in 6 fractions and cyclophosphamide 50 mg/kg daily for 3 days as conditioning. There were 58 sibling transplants and 14 unrelated donor transplants. Stem cell source for all alloSCT was bone marrow. Source of autografts were purged bone marrow using either 4-hydroxpercyclophosphamide (4-HC) or mafosfamide (n = 25), and unpurged PBSC (n = 61). PBSCs were mobilized with cyclophosphamide (2.5-7.0 g/m^2) followed by granulocyte colony-stimulating factor (G-CSF). Patients in the ASCT group were offered maintenance treatment with interferon 3 million units 3 times a week posttransplant until relapse or intolerance. Fifty-eight patients agreed to receive interferon.