Trends and Outcomes in Allogeneic Hematopoietic Stem Cell Transplant for Multiple Myeloma at Mayo Clinic

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Abstract

Allogeneic transplant for myeloma remains controversial at best. We have reviewed more than 20 years of experience at Mayo Clinic to report our outcomes in a mostly relapsed/refractory population in a nontandem setting. Hardly justifiable as front-line, the long-term survival rate was 20% for the end-of-the-line option.

Background: Allogeneic transplant in myeloma remains controversial. **Patients and Methods:** We performed a retrospective review of 76 patients in the Mayo Clinic database from 1993 to 2013 who underwent allogeneic hematopoietic stem cell transplant (HSCT) for myeloma. **Results:** After excluding ineligible patients, among the remaining 66 patients, median age at transplant was 42 years and 87% had residual disease at the time of transplant. Myeloablative (71%) versus reduced intensity conditioning (29%), matched sibling donors (70%) versus unrelated donors showed no outcome difference. Median overall survival from the time of diagnosis and transplant were 75 and 24 months, respectively. Median time to disease progression (TTP) was 15 months and treatment-related mortality was 20% at day 100. Acute and chronic graft versus host disease (cGVHD) developed in 61% and 48% patients, respectively. In univariate analysis of overall survival (OS), factors predicting adverse outcome were pretransplant 24-hour total urinary protein ($P = .035$), peripheral blood versus bone marrow (OS 18 vs. 41 months; $P = .02$), number of previous therapies ($P = .014$), time from autologous to allogeneic HSCT ($P = .019$), and cGVHD ($P = .01$). TTP was adversely affected by number of previous regimens ($P = .036$) and PB as graft source ($P = .016$). In multivariate analysis for progression-free survival, number of previous regimens ($P = .04$), and for OS, time between autologous and allogeneic HSCT was significant ($P = .009$). **Conclusion:** In 162 matched control subjects who were human leukocytoe antigen-typed, there were no survivors at 12 years compared with 20% in the group who received a transplant. In a second control group with 197 second autologous transplants, 10-year OS was 8%.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 6, 349-57
Keywords: Allogeneic transplant, Multiple myeloma outcomes

Introduction

A cure for multiple myeloma (MM) remains elusive.[1] Achieving a complete response (CR) is not synonymous with cure, particularly for aggressive disease.[2] In an era that investigated minimal residual disease monitoring of myeloma with multicolor flow cytometry and other sensitive techniques such as deep sequencing, even stringent CR no longer represents a cure.[3-5] Introduction and widespread use of newer agents including proteasome inhibitors and immunomodulatory agents has resulted in significant improvements in survival.[6-10] Autologous transplantation after high-dose melphalan-based chemotherapy has been a standard option for myeloma patients with good performance status and MM remains the most common indication for autologous transplant.[11] However, relapse remains a concern because of the inability of current therapies to completely eradicate myeloma cells in the patient and the graft.[12]

Allogeneic transplant has been attempted in myeloma since the early 1980s.[13] Because reduced-intensity conditioning (RIC)

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Submitted: Jan 13, 2015; Revised: Mar 23, 2015; Accepted: Mar 26, 2015; Epub: Apr 2, 2015

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.03.016

Table 1 Characteristics of Patients Who Underwent Allogeneic HSCT for MM at Mayo Between 1993 and 2013 (n = 66)

Recipient Demographic Characteristics	n or Median (% or Range)
Age at Time of Transplant, Years	48 (28-61)
Male Sex	42 (63)
Caucasian Race	61 (92)
Myeloma Variables	
IgG subtype	39 (59)
IgA subtype	7 (10)
Light chain	18 (27)
Nonsecretory/biclonal	2 (3)
DS stage III	27 (56)
Missing	23
Cytogenetics Abnormal/ Missing	10 (29)/35
FISH High Risk/Missing	8 (32)/45
BJ Protein κ Versus λ	31 versus 19 (48 vs. 29)
BM Plasma Cells %	60 (1-95)
Recipient Transplant Variables	
Number of Previous Chemotherapies Excluding Autologous HSCT	3 (1-8)
Previous Autologous HSCT	50 (76)
Time Diagnosis to Allogeneic HSCT, Months	33 (3-181)
Time First Autologous to Allogeneic HSCT, Months	22 (0.73-84)
Conditioning Myeloablative/ Reduced Intensity	47 (71)/19 (29)
Flu-Mel	9 (13)
Mel-TBI	32 (48)
Bu-Cy	2 (3)
Cy-TBI	9 (13)
Flu-Cy	1
Flu-TBI	7 (11)
Mel	2 (3)
2CDA/TT/ATG	4 (6)
GVHD Prophylaxis	
Cyclosporine-based	45 (68)
Tacrolimus-based	16 (24)
None/missing	5 (8)
Disease Status at Time of Transplant	
Relapsed/refractory/ progression	29 (44)
PR/CR	37 (56)
Donor Variables	
Age	44 (19-70)
Male sex	29 (43)
Parity	0 (0-7)
ABO mismatch	31 (47)
HLA mismatch	3 (5)
Matched sibling versus other (haplo, MUD)	46 (70) versus 20 (30)- (MUD 18/haplo 2)
PB Versus Marrow Harvest	49/17 (74/26)

Abbreviations: ATG = Anti Thymocyte Globulin; BJ = Bence Jones; BM = Bone Marrow; Bu = Busulfan; 2CDA = 2Cladribine; Cy = Cyclophosphamide; DS = Durie-Salmon Stage; FISH = fluorescence in situ hybridization; Flu = Fludarabine; GVHD = graft versus host disease; haplo = Haploidentical; HLA = human leukocytoe antigen; HSCT = hematopoietic stem cell transplant; Mel = Melphalan; MM = multiple myeloma; MUD = Matched Unrelated Donor; PB = peripheral blood; TBI = Total Body Irradiation; TT = Thiotepa.
[a]Excludes 4 syngeneic.

allogeneic transplant usually is not a good cytoreductive strategy, a preceding autologous transplant has been hypothesized to achieve major cytoreduction and allow a subsequent allograft to exert a graft versus myeloma (GVM) effect.[14]

The value of allogeneic hematopoietic stem cell transplant (HSCT) in the proteasome inhibitor/immunomodulatory drug era has been questioned[15,16] however, the 2 approaches are not mutually exclusive.[17,18] Indeed, it has been suggested that the introduction of newer agents before allogeneic HSCT allows better disease control resulting in improved outcomes after allogeneic transplantation.[19] Ongoing studies are investigating proteasome inhibitors in conditioning regimens[20] and for treatment of graft versus host disease (GVHD).[21]

Allogeneic HSCT is potentially curative, suggested by a plateau effect in survival at approximately 6 years,[22] but is constantly being pushed to an end-of-the-road option despite the availability of matched sibling donors.[23] Although it has been abandoned at some centers as an option because of high treatment-related mortality (TRM), in some studies 30% to 40% for myeloablative conditioning,[24,25] others have contested it as an underused modality in eligible patients using the Surveillance, Epidemiology, and End Results database by highlighting that only 11% of eligible patients received a transplant in the period from 2004 to 2008.[26]

Patients with high-risk cytogenetics and aggressive disease continue to break through currently available agents making allogeneic HSCT an attractive option for disease control.[27] In high-risk myeloma based on fluorescent in situ hybridization (FISH) abnormalities such as 17p deletion, t (4; 14), t (14; 16), and t (14; 20), an allogeneic approach might have a role.[28,29] Duration of remission after a first autologous transplant also factors in the decision to proceed to allogeneic HSCT because the benefit of a second autologous transplant within 1 year of a failed first transplant is likely marginal.[30]

The International Myeloma Working Group (IMWG) 2010 recommendations justify RIC allogeneic transplant in myeloma only in the context of clinical trials.[31] Needless to say, this remains a controversial option at best and more data need to be reported.

In this study, we attempted to determine the place of allogeneic transplant for myeloma in the present-day treatment algorithm by assessing outcomes and treatment-related complications from a prospectively maintained database at our institution.