Biol Blood Marrow Transplant 21 (2015) 468–472

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Second Autologous Stem Cell Transplant: An Effective Therapy for Relapsed Multiple Myeloma

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Article history:
Received 21 July 2014
Accepted 13 November 2014

Key Words:
Multiple myeloma
Relapsed
Autologous stem cell transplant
Melphalan

A B S T R A C T

Therapeutic options for patients with multiple myeloma (MM) whose disease has relapsed after a prior autologous stem cell transplant (ASCT) include an expanding armamentarium of novel agents, often combined with traditional chemotherapy, or a second ASCT, with no clear standard of care. We retrospectively analyzed the outcomes of 75 patients who underwent salvage melphalan-based ASCT for relapsed MM at Memorial Sloan-Kettering Cancer Center between 1995 and 2012. Conditioning was performed with melphalan 200 mg/m^2 (n = 43), 180 mg/m^2 (n = 1), 140 mg/m^2 (n = 22), and 100 mg/m^2 (n = 9). The median age at second ASCT was 59 years (range, 36 to 75), and 58% (n = 35) were men. Of those with available data, 19% had high-risk cytogenetics (including t (4;14), p53 loss, or del 13q by karyotype) at the time of second ASCT. Median interval between first and salvage ASCT was 37.5 months (range, 6.9 to 111.4). Of 72 assessable patients, 57% had chemotherapy-sensitive disease before to salvage ASCT and 43% were chemoresistant. Four patients died within 100 days of ASCT. Response was assessed at 2 to 3 months post-ASCT, and of 71 assessable patients, 82% achieved at least a partial response, 15% had stable disease, and 3% progressed despite salvage ASCT. After salvage ASCT, 38 patients received maintenance therapy and 14 went on to allogeneic ASCT. The median progression-free survival (PFS) after second autograft was 10.1 months (95% confidence interval [CI], 7.6 to 13.4) and median overall survival (OS) 22.7 months (95% CI, 19.2 to 41.2). Patients with chemosensitive relapse had a trend toward better PFS (hazard ratio [HR], .60 [95% CI, .36 to 1.02]; $P = .058$) and significantly longer OS (HR, .49 [95% CI, .27 to .88]; $P = .017$) than patients with resistant relapse. Those with high-risk cytogenetics at the time of second ASCT had higher risk of death (HR, 2.98 [95% CI, 1.28 to 6.97]; $P = .012$) compared with patients with standard-risk cytogenetics. Salvage ASCT is an effective strategy for relapsed MM with chemosensitive disease and results in comparable PFS and OS to other salvage strategies.

INTRODUCTION

An increase in available and effective therapies for patients with multiple myeloma (MM) has led to an improvement in overall survival (OS) [1]. High-dose therapy and autologous stem cell transplant (ASCT) as part of initial therapy is complementary to novel therapies and represents a standard for patients with MM younger than 65 years and selected cases older than this age [2,3]. However, almost all patients with MM will relapse after initial therapy, and most patients with MM still die of their disease. The median time to progression after initial ASCT is 23 to 46 months and is longer for patients who receive post-transplant maintenance therapy [4-9]. At the time of disease recurrence, no 1 standard salvage approach is used; instead, various therapeutic options are used, including retreatment with prior effective therapy, use of novel or experimental agents, and, in selected patients, allogeneic (allo-) SCT.

The first report of the use of ASCT as salvage therapy was published in 1995 and demonstrated a significantly prolonged survival compared with standard therapy [10]. Reported rates of progression-free survival (PFS) after second salvage ASCT have differed and have ranged from a median of 6.8 months to 4.2 years [11,12]. Here, we report the results of a retrospective analysis of salvage ASCT conducted at our center. Our goal was to define the outcomes of patients with access to more modern therapy who underwent salvage ASCT and to identify prognostic factors for prolonged PFS and OS.

Financial disclosure: See Acknowledgments on page 472.

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http://dx.doi.org/10.1016/j.bbmt.2014.11.677
1083-8791/

Table 1
Patient Characteristics/Clinical Factors at Second ASCT and Management after Second ASCT

Characteristics at Second ASCT	n	%
Risk (27 missing)		
High risk	9	19
None high risk	39	81
ISS stage (8 missing)		
I	34	51
II	20	30
III	13	19
Melphalan dosing		
100	9	12
140	22	29
180	1	1
200	43	57
Neoadjuvant chemotherapy (3 N/A)		
Resistant	31	43
Sensitive	41	57
Time to relapse after first ASCT		
Within 1 yr	12	16
≥1 yr	62	84
	Median	Range
Age, yr	59	36-75
Albumin	3.7	2.0-4.6
β_2-micro	2.3	0-28.8
LDH	176	96-1893
Months between first and second ASCT	37.5	6.9-111.4
Time to relapse after first ASCT, mo	21.9	2.7-136.2
Management post salvage ASCT	n	%
Maintenance therapy (5 N/A)		
Yes	38	51
No	37	49
Allo-ASCT (nonmaintenance)		
Yes	14	19
No	61	81

ISS indicates International Staging System; N/A, not available; β_2-micro, Beta-2 microglobulin; LDH, lactate dehydrogenase.

METHODS

Patients

With institutional review board approval, we performed a systematic, retrospective review of medical charts of all patients who received salvage ASCT for MM at Memorial Sloan-Kettering Cancer Center between 1995 and December 2012. In total, 75 patients were identified.

Definitions

A transplant was defined as salvage if the patient had already received a prior ASCT and underwent a second ASCT after evidence of disease progression, regardless of the number of lines of treatment administered after the first ASCT. Patients who received a planned tandem ASCT were excluded from this study. PFS was defined as the time from date of the second ASCT to disease progression or death, whereas OS was defined from the date of the second ASCT to the date of death from any cause. Patients with high-risk cytogenetics were defined by the presence of t (4;14), del p53, and del13q by karyotype only. Chemotherapy-sensitive disease was defined by having achieved at least a minimal response (25% reduction in serum M-protein level or 50% reduction in urine M-protein) to salvage chemotherapy before second ASCT.

Response

Response and progression were defined according to the International Myeloma Working Group criteria [13,14]. A complete response was defined as negative immunofixation of serum and urine, disappearance of soft tissue plasmacytoma, and <5% plasma cells in the bone marrow. Very good partial response was defined as serum and urine M-protein detectable only by immunofixation or as a 90% or greater reduction in serum M-protein plus a urine M-protein level <100 mg per 24 hours. Partial response was defined as a reduction in serum M-protein of at least 50% and by a reduction of at least 90% or an absolute value <200 mg per 24 hours in urine M-protein. Minimal response was defined by reduction in the serum M-protein by at least 25% but less than 50% and reduction in the urine M-protein by 50% to 89%. Stable disease was defined as not meeting any response criteria, and progressive disease was defined as a confirmed increase >25% of M-protein from baseline. Relapse was defined as the reappearance of serum or urine M-protein or the development of new bone lesions, plasmacytoma, or hypercalcemia. Response post-ASCT was assessed at a maximum of 80 to 100 days post-transplantation, and patients were followed approximately every 3 months thereafter.

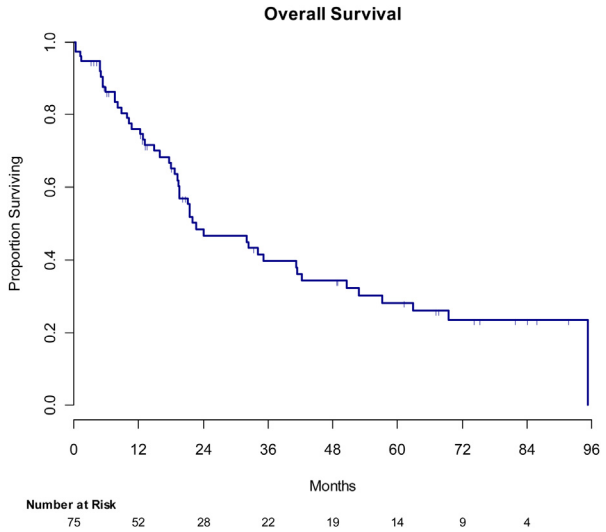

Figure 1. OS for MM patients undergoing a second ASCT.

Statistical Analysis

Cox proportional hazard model was used to assess the associations between the following variables collected before second ASCT with OS and PFS: time to relapse after first ASCT, time between first and second ASCT (≥18 months versus <18 months), the presence of high-risk cytogenetics, and chemosensitive disease. Time-dependent Cox regression was used to evaluate the post-second ASCT factors of maintenance therapy and allo-ASCT after second ASCT. Univariate factors significant at the .05 level were included in multivariate models for OS and PFS. Survival curves of patients were prepared using the Kaplan-Meier method.

RESULTS

Patient Characteristics

Patient characteristics at time of second transplants are shown in Table 1. In total, 75 patients (45 men and 30 women) received second ASCT for relapsed MM at our center from January 1998 to December 2012. Median age at second transplant was 59 years (range, 36 to 75). The median time to relapse after first ASCT was 21.9 months. The median number of months between first and second transplant was 37.7 (range, 6.9 to 111.4). Median number of chemotherapies before second transplant was 1 (range, 1 to 4). Sixteen patients had 2 lines of therapies before transplant, 12 patients had 3 lines, and 5 patients had 4 lines of therapies before transplant. The most likely explanation for this could be physician's discretion to take the patient to transplant even if they were not responding to salvage therapy.

In total, 31 patients had resistant/refractory disease going into the transplant. Of these 31, 12 patients were treated with a single line of therapy before transplant consisting of agents either alone or in combination (eg, thalidomide, Decadron, velcade, Cytoxan, cisplatin, etoposide, and revlimid). Eight patients had 2 lines of treatment, 7 patients had 3 lines of treatment, and 4 patients had 4 lines of treatment. Of patients with available data, 19% had high-risk disease at time of second transplant. Thirty-eight patients (51%) received thalidomide, lenalidomide, or bortezomib maintenance therapy after the second transplant. Fourteen patients (19%) received allo-ASCT after their second autologous transplant.