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Review Article

Predictive Factors for the Outcome of Salvage Autologous Stem Cell Transplant in patient with Relapsed Multiple Myeloma

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Abstract

Background: There is no clear standard of care for patients with multiple myeloma whose disease has relapsed after a prior autologous SCT. Limited data are available regarding the value of salvage auto-SCT, and the factors that determine the outcome have not been well described.

Methods: We retrospectively reviewed our experience at Saskatoon Cancer Center with salvage auto-SCT for relapsed multiple myeloma, looking at the outcome and the determining variables that could affect this outcome. Thirty three patients had received a salvage auto-SCT at our institution between; February 2000 to February 2012.

Results: Median age at salvage auto-SCT was 60 years (range; 46-71). Median time to relapse after the first auto-SCT was 32 months. Only 30% of the patients received more than 2 lines prior to salvage auto-SCT. Overall response at day 100 after salvage auto-SCT was 93 % and non relapse mortality was 3 %. With a median follow up of 24 months, the median progression free survival (PFS) was 27 months and the median overall survival (OS) was 36 months. Patients who had received < 2 lines of therapy prior to salvage auto-SCT had significantly longer median PFS of 31 and OS of 52 months, compared to 19 and 33 months for patients who had received ≥2 lines of therapy. Patients who had relapsed more than 2 years post 1st SCT had a significantly longer median PFS and OS of 27 and 39 months compared to 22 and 24 months respectively in patients who had relapsed < 2 years.

Conclusion: Salvage auto-SCT is a safe and effective alternative therapy for patients with relapsed multiple myeloma. Patients received several lines of therapy and their disease progressed in less than 2 years from the initial SCT are unlikely to benefit significantly. Therefore, salvage auto-SCT should be considered as appropriate option for selected patients with relapsed multiple myeloma.

Keywords: Multiple Myeloma; Transplantation; Salvage Therapy; Auto-SCT; Toxicity; Predictive Factors

Abbreviations

CR : Complete Response;

PR : Partial Response;

VGPR : Very Good Partial Response;

TTP : Time To Progression;

OS : Overall Survival;

TTP : Time To Disease Progression;

TRM : Treatment-Related Mortality;

ISS : International Scoring System;

ANC : Absolute Neutrophil Count

Introduction

Multiple myeloma is one of the most common hematologic malignancies in adults. In the United State, it is estimated that 24,050 patients will be newly diagnosed and 11,090 patients will die of multiple myeloma in 2014 [1].

Autologous stem-cell transplant is considered the standard of care for patients less than 70 years of age at time of transplant. Several randomized trials demonstrated the superiority of autologous stem-cell transplant over conventional chemotherapy in terms of the response rate and event-free survival. However, the median duration of response after this procedure does not exceed three years, and almost all patients ultimately relapse [2-5].

Therapeutic options for patients with relapsed multiple myeloma has increased significantly in recent years. Novel agents such as thalidomide, lenalidomide and bortezomib have been studied extensively in the salvage setting; however, prolonged treatment can result in significant toxicities, and the PFS (PFS) in a majority of patients with persistent or refractory disease is only 6 to 14 months [6].

The efficacy and safety of salvage auto-SCT for relapsed patients, particularly in the era of novel therapeutics, is unclear. Several studies suggest that salvage auto-SCT is reasonably safe for selected patients and may grant additional PFS ranged from a median of 6.8 months to 4.2 years [7-11]. However, many of these studies contain small numbers of patients and have variable duration of follow-up; the true benefit of salvage auto-SCT for relapsed multiple myeloma is therefore not well defined.

In this study, we retrospectively reviewed our experience at Saskatoon Cancer Centre with salvage auto-SCT for relapsed multiple myeloma patients to explore the factors that may predict a successful outcome, with a better PFS and OS.

Patients and methods

Patients

From a prospectively collected database of the Saskatoon Cancer Centre, thirty three patients with relapsed multiple myeloma who received salvage auto-SCT between February 2000 and February 2012 were reviewed. All patients signed written informed consent according to our institutional and National Marrow Donor Program guidelines. Data of this retrospective study were abstracted from the database and patient medical records, according to protocols approved by the University of Saskatchewan Biomedical Research Ethics Board.

Eligible patients had a diagnosis of multiple myeloma and had evidence of relapse after having undergone an auto-SCT. Patients who received second transplant as part of a planned tandem auto-SCT were excluded from this study. In general, patients were eligible to receive the second transplant if the first transplant was not associated with severe regimen-related toxicity. In addition, an Eastern Cooperative Oncology Group performance status of < 2 and had adequate renal (creatinine < 200 umol/L), cardiac (left ventricular ejection fraction > 45%), pulmonary (diffusing capacity of the lung for carbon monoxide > 50%), and hepatic (bilirubin, transaminases < 2 x upper limit of normal) function. Patients older than 65 years with a good performance status were also eligible for transplantation.

Methods

A transplant was considered as salvage if the patient had already received a prior auto-SCT and underwent a second auto-SCT after disease progression. Definitions of response and progression were used according to the updated European Group for Blood and Marrow Transplantation Criteria [12]. Response was assessed at day 100 after the salvage auto-SCT. All response categories required 2 consecutive assessments. Responses were categorized as complete response (CR) if there was disappearance of monoclonal protein in the serum and urine by immunofixation, disappearance of any soft tissue plasmacytoma, and < 5% plasma cells in bone marrow as well as normalization of the free light chain ratio. Very good partial response (VGPR) was defined as serum and urine monoclonal protein detectable by immunofixation but not by electrophoresis, or > 90% reduction in the monoclonal protein in the serum plus < 100 in the 24 hours urine. Partial response (PR) was defined as > 50 % decrease in the monoclonal protein in the serum, > 90% decrease in the monoclonal protein in the urine, > 50% decrease in the soft tissue plasmacytoma, and in the plasma cells in bone marrow. Progressive disease (PD) was defined as > 25% increase in the monoclonal protein or in the plasma cell in the bone marrow, or in the soft tissue plasmacytoma, or development of new lesions.

Neutrophil engraftment was defined as the first date of 3 consecutive laboratory values with absolute neutrophil count (ANC) > 0.5 x 10^9/L. Platelet engraftment was defined as the first date of 3 consecutive laboratory values with a platelet

count of > 20 x 10^9/L without platelet transfusion 7 days prior. Failure to engraft by day 30 was considered primary graft failure.

Adverse effects were graded according to current National Cancer Institute Common Toxicity Criteria [13].

All patients received peripherally collected stem cells that had been collected and cryopreserved before their first auto-SCT, using standard mobilization protocol Cyclophosphamide / G-CSF and aphaeresis technique [14].

Conditioning regimen for the salvage auto-SCT was high dose melphalan alone (200 mg/m^2); Patients received infection prophylaxis with ciprofloxacin, fluconazole, and acyclovir or valacyclovir. Filgrastim 5µg/kg was administered subcutaneously daily from day +7 after auto-SCT until the recovery of ANC to > 0.5 x 10^9/L for 3 days. Blood products were irradiated and filtered to remove leukocytes before transfusion. After recovery of neutrophil count, patients received infection prophylaxis with sulfamethoxazole- trimethoprim or pentamidine.

Statistical Methodology

Primary endpoints were Kaplan-Meier estimates of OS and PFS. Secondary endpoints were response rate, treatment-related mortality (TRM), and toxicity rates. OS was measured from the day of autologous stem cell infusion (day 0) to death from any cause, with censoring performed at the date of last contact. PFS was determined from the day of stem cell infusion to the day of documented relapse or progression. Death from any cause other than relapse before day 100 was classified as TRM. Patient characteristics were summarized using the median (range) for numerical variables or frequencies (percentages) for categorical variables. The Cox proportional hazards model was used to perform univariate analyses of possible prognostic variables for PFS and OS, after confirming the proportionality of each variable using time-dependent covariate. Only predictive variables with a significant result ($p < 0.05$) in univariate analysis entered multivariate Cox analysis using backward stepwise selection methods. The log-rank test for equality of survivor functions was used to detect differences across ordered categories. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patients Characteristics

Between February 2000 and February 2012, Thirty three patients had received a salvage auto-SCT for relapsed multiple myeloma at our institution. Patient characteristics are shown in Table 1. Of the 33 patients, 22 (67%) were men, and 11(33%) were women. The median age at diagnosis was 57 years (range 45–67). Thirteen patients (42%) had chromosomal abnormalities on conventional cytogenetic studies. Patients received a median of 2 lines of therapy prior to the initial auto-SCT (range 1–4); the median time from diagnosis to initial auto- SCT was 7 months (range 5–20). Twenty two patients (67%) had achieved CR after the initial auto-SCT. The median time to disease progression (TTP) after initial auto-SCT was 32 months (range 3–80).

Table 1. Patient characteristics.

Variable	Number (range or percent) or median (range) (n = 33)
Gender	22 (67%) male, 11(33%) female
Age at diagnosis	57 years (45–67)
Ig subtype:	
IgG	23 (74%)
IgA	4 (13%)
κ -Light chain	4 (13%)
λ -Light chain	2 (7%)
International Scoring System:	
I	15 (48%)
II	13 (24%)
III	5 (16%)
Lytic Lesions	30 (97%)
Plasmacytoma	10 (32%)
Cytogenetics:	
Normal	16 (52%)
Abnormal	13 (42%)
Missing	4 (13%)
Age at initial auto-SCT	58 years (46–68)
Duration from diagnosis to initial auto-SCT	7months (5–20)
Response to initial auto-SCT:	
CR	21 (64%)
PR	12 (36%)
TTP after initial auto-SCT	32 months (3–80)
Age at second auto-SCT	60 years (46–71)
Time from first to second auto-SCT	35 months (3–86)
Number of prior lines of therapy	1 (0–3)
Novel therapies prior to second auto-SCT:	
Prior thalidomide	2 (6%)
Prior lenalidomide	2 (6%)
Prior bortezomib	12 (36%)
Responding disease prior to second auto-SCT	27 (82%)
Response to second auto-SCT:	
CR	7 (21%)
VGPR	10 (30%)
PR	14 (42%)
Could not be assessed	2 (6%)
Treatment-related mortality	1 (3%)
Duration from diagnosis to second auto-SCT	44months (9–95)
TTP after second auto-SCT	27 months (1–89)
OS after second auto-SCT	36 months (1–99)

Abbreviations: CR = complete response, PR = partial response, VGPR = very good partial response, TI time to progression, OS = overall survival

Salvage Auto-SCT

Median age at the time of salvage auto-SCT was 60 years (range 46–71). The median time from diagnosis to salvage auto-SCT was 44 months (range 9–95), and the median time interval between the first and second auto-SCT was 35 months (range 3–86). Prior to the salvage auto-SCT, 13 of 33 patients (39%) had been treated with novel agent; 12 patients (36%) had been treated with bortezomib, 2 patients (6%) with thalidomide and another 2 patients with lenalidomide, the rest received re-induction with conventional chemotherapies. The median number of prior lines of therapy before salvage auto-SCT was 1 (range 0–3), with 23 patients (70%) had received less than 2 lines and 30% received more than 2 lines. Twenty seven patients (82%) had responsive disease at the time of salvage auto-SCT. During the salvage auto-SCT the patients received CD34+ cells in a median of 5.5 x 10^6 /kg (range 2.2-10 x 10^6/kg), which had been collected and cryopreserved before the first Auto-SCT.

Engraftment and toxicity

Median time to neutrophil and platelet engraftment after the salvage auto-SCT was 11 days (range 6-14 days and 2-15 days) respectively. The median duration of hospital stay was 16 days (range 13-36 days).

The non hematological toxicity was moderate. The most common grade 3 and 4 toxicities were febrile neutropenia 64%, mucositis 33%, diarrhea 28%, renal impairment 6%, hepatic impairment 3%, cardiac adverse events 12%, and deep venous thrombosis 9%. There was one transplant-related death (3%) from sepsis and pulmonary embolism (Table 2).

Table 2. Grade 3 and 4 Adverse Event during Salvage Auto-SCT.

Adverse Event	Patients No. (%)
Cardiovascular	
Pulmonary edema	3 (9%)
Arrhythmia	1 (3%)
Deep venous Thrombosis	3 (9%)
Gastrointestinal	
Mucositis	11 (33%)
Diarrhea	9 (28%)
Neutropenic fever	21 (64%)
Renal	2 (6%)
Hepatic	1 (3%)

Response and Survival

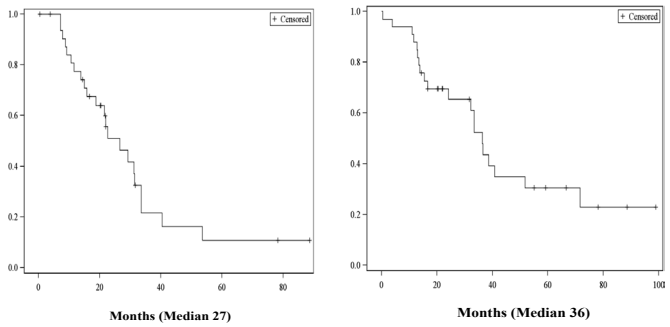
Overall response rate was (93%). Seven patients (21%) achieved CR, 10 patients (30%) had a very good partial response and 14 patients (42%) had partial response. Two patients were not evaluated, one patient died within 100 days of salvage auto-SCT and the other patient died at Day 105 secondary to acute renal failure and atrial fibrillation. With a median follow-up of 24 months (range 1-99) after the salvage auto-SCT, the median PFS was 27 months (range 1–89) and the median OS was 36 months (range 1 – 99; Figure 1). Eleven of 33 patients had a TTP inversion (PFS longer after the second transplant) with a median increase of 18 months, only two of them received novel agents, 70 % required less than two lines prior to salvage SCT, and seven patients had complete remission after the salvage SCT. After a median follow-up of 74 months (> 6 years) since the initial diagnosis, 13 patients (39%) were alive, 8 of them did not show any disease progression. The median OS was 97 months (> 8 years).

Predictive Factors

In univariate analysis, looking at prognostic variables for survival benifit after salvage auto-SCT, several factors were examined include: age at the time of salvage auto-SCT, response to initial auto-SCT, TTP after initial auto-SCT, time interval between the first and second transplants, number of prior lines of therapy, prior novel therapies (thalidomide, lenalidomide, bortezomib), responsive disease at the time of salvage auto-SCT, and abnormal cytogenetics.

Patients who had received novel therapy prior to the salvage SCT (13/33) had a longer median TTP and OS of 23 and 36months respectively compared to 22 and 35 months in patients who hadn't received novel therapy (20/33; P= 0.6 and 0.83 respectively).

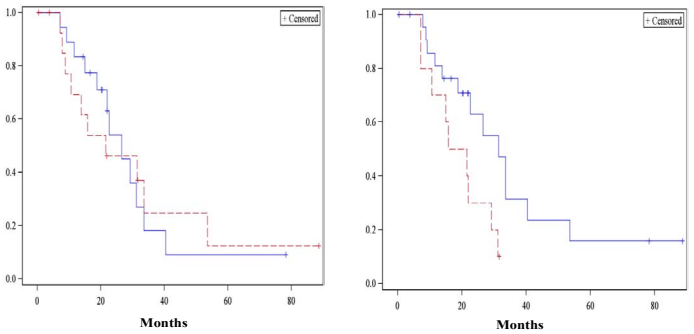
Figure 1. Progression free (left) and overall survival (right) after salvage Auto-SCT.



The response to salvage auto-SCT has an impact on OS and TTP. Patients achieved CR or VGPR after 2nd SCT (17/33) had a longer median TTP and OS of 27 and 52 months respectively compared to 19 and 32 months in patients who had PR (14/33; P= 0.21and 0.24, respectively).

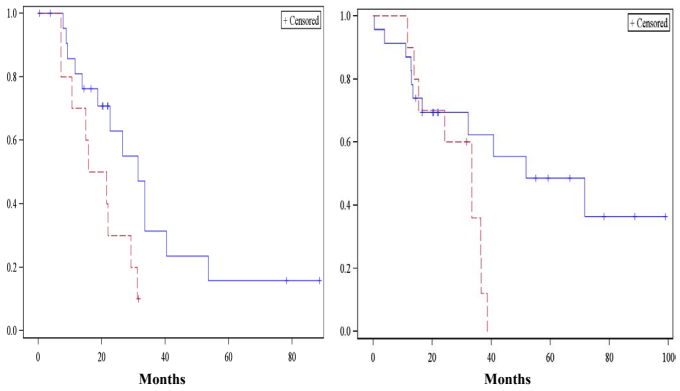
Patients who had duration of remission more than 2 years following 1st SCT had a significantly longer median TTP and OS of 27 and 39 months respectively. In contrast to 22 and 24 months in patients who had disease progression less than or equal to 2 years after 1st SCT (P= 0.91 and 0.14, respectively; Figure 2).

Figure 2. Progression free (left) and overall survival (right) after salvage Auto-SCT stratified by time of relapse after the up-front Auto-SCT (-----> 24,----≤ 24 Months).



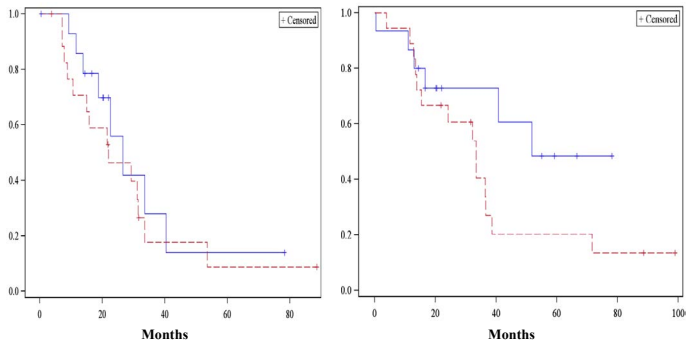
Patients who had received < 2 lines of therapy prior to salvage auto-SCT had significantly longer median TTP of 31months, and OS of 52 months, compared to 19 and 33 months respectively for patients who had received ≥ 2 lines of therapy (P = 0.04; Figure 3).

Figure 3. Progression free (left) overall survival (right) after salvage Auto-SCT stratified by number of prior lines of therapy (----< 2,--- ≥ 2).



In univariate analysis only TTP after the 1st SCT and the number of lines prior to salvage auto-SCT had a significant impact on the outcome of the salvage auto-SCT. By categorizing the patients according to these two factors, two groups could be identified: Patients who had TTP after the 1st SCT > 24 months, and received < 2 lines of therapy prior to salvage auto-SCT. The second group; patients who had either TTP after 1st SCT less than 24 months, or received > 2 lines prior to salvage auto-SCT. The median OS was 52 and 33 months, respectively (P= 0.12) and the median PFS was 27 and 22 months, respectively (P= 0.4; Figure 4).

Figure 4. Progression free (left) and overall survival (right) after salvage Auto-SCT stratified by prognostic factors.



In multivariate analysis, only response to salvage SCT > PR had an impact on TTP and OS; however it was not statistically significant.

Discussion

To our knowledge, there is no standard salvage treatment for patients with multiple myeloma who relapsed following initial auto-SCT. Treatment options include novel agents, conventional chemotherapy, salvage auto-SCT and allogeneic transplants.

Data evaluating the role of salvage auto-SCT are limited; several small retrospective analyses have demonstrated that it is an effective and well tolerated treatment option with overall response rates reported between 55-90%. In our single center experience of 33 patients, salvage auto-SCT appears to be a safe and effective treatment for patients who relapsed after initial auto-SCT. Our survival and toxicity data are comparable to published and preliminary reports from several other institutions with similar sample sizes [10, 11, 15-17].

Our group of patients was heavily pretreated, as all patients had a prior transplant, 70% received more than two lines prior to salvage auto-SCT and 40% were previously treated with novel agents. However, our patients had a median age of 60 years, 72% of patients presented with international scoring system (ISS) stage I or II, and thus had a better prognostic profile than usually reported for patients within salvage studies. Transplant-related mortality was 3%which is comparable to that reported with first auto-SCT [2, 3].

The overall response rate (CR, VGPR, and PR) after the salvage auto-SCT in our study was 93% including 51% of patients who achieved complete or very good partial response. These results compare very favorably with the overall response rates observed with novel agents such as thalidomide, lenalidomide or bortezomib, which are between 30-60%. After a median follow-up of 24 months, the median PFS after salvage auto-SCT was 27 months, and the median OS was 36 months which is considerably higher than the data observed with the novel agents 6-12 months and 12-30 months respectively [18-21].

Because of limited efficacy, long term treatment duration, and treatment-related complications of salvage auto-STC is a feasible option compared to conventional nontransplant approaches using newer agents. However further large randomized trials are warranted. The value of salvage auto-SCT at relapse, as compared with an upfront tandem transplant, is unknown. Preliminary results from a randomized trial show no difference in OS; however, longer follow-up is needed [22].

In this study the OS and PFS after salvage auto-SCT is significantly improved for patients who have experienced a late disease relapse (more than 2 years) after the initial auto-SCT, irrespective of subsequent therapies given at relapse (although it is not statistically significant). However, the length of time which constitutes a late relapse has varied between studies, ranging between 12 months and > 36 months. A recently published retrospective review showed that patients who relapsed less than 24 months of initial auto-SCT had significantly shorter OS compared to those who relapsed more than 24 months (28.47 months vs. 71.3 months) [16].

Our data suggest that the receipt of multiple prior lines of therapy (>2) is another poor prognostic factor. OS and PFS are significantly improved for patients who have received fewer lines of therapy prior to salvage auto-SCT. This can be explained by the presence of chemoresistant disease or the persistence of residual toxicities from prior therapies.

The limitations of this study include several factors: It is retrospective in nature, limited in sample size, distributed over 12 years, and confers some selection bias; more favorable patients were likely recommended for salvage auto-SCT, thus these results may not be applicable to all patients.

We conclude that salvage auto-SCT generally appears to be a safe and effective treatment for selected patients with relapsed multiple myeloma. Patients who received more than two prior lines of therapy, and/or their disease progressed within less than two years after initial transplant are unlikely to benefit significantly. Further prospective randomized control trials are needed to optimize treatment for this group of patients.

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Competing interests

The authors have no financial or non-financial interests in relation to the manuscript to disclose.

Authors' contributions

M Emara has made contribution to conception and design; data collection, analysis and interpretation; drafting and final approval of the version to be published. A Sharma has made substantial contributions in data extraction. S Sarker and R Alvi have been involved in data analysis. W Sabry and J Stakiw have been involved in the critical revision. H Goubran made critical revision and approved final version. M Elemary has made contribution to conception and design, interpretation of the data and final approval of the manuscript. All authors reviewed and approved of the final manuscript.

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