Biol Blood Marrow Transplant 24 (2018) 1372–1378

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Autologous

Outcome of a Salvage Third Autologous Stem Cell Transplantation in Multiple Myeloma

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Article history:
Received 5 November 2017
Accepted 26 January 2018

Key Words:
Multiple myeloma
Relapse
Autologous hematopoietic cell transplantation

A B S T R A C T

To evaluate the outcomes of salvage third autologous stem cell transplantation (ASCT) in patients with relapsed multiple myeloma. We analyzed 570 patients who had undergone a third ASCT between 1997 and 2010 (European Society for Blood and Marrow Transplantation data), of whom 482 patients underwent tandem ASCT and a third ASCT at first relapse (AARA group) and 88 patients underwent an upfront ASCT with second and third transplantations after subsequent relapses (ARARA group). With a median follow-up after salvage third ASCT of 61 months in the AARA group and 48 months in the ARARA group, the day +100 nonrelapse mortality in the 2 groups was 4% and 7%, the incidence of second primary malignancy was 6% and 7%, the median progression-free survival was 13 and 8 months, and median overall survival (OS) was 33 and 15 months. In the AARA group, according to the relapse-free interval (RFI) from the second ASCT, the median OS after the third ASCT was 17 months if the RFI was <18 months, 37 months if the RFI was between 18 and 36 months, and 64 months if the RFI was ≥36 months ($P < .001$). In the ARARA group, the median OS after the third ASCT was 7 months if the RFI was <6 months, 13 months if the RFI was between 6 and 18 months, and 27 months if the RFI was ≥18 months ($P < .001$). In a multivariate analysis of the AARA group, the favorable prognostic factor was an RFI after second ASCT of ≥18 months. Progressive disease and a Karnofsky Performance Status

Financial disclosure: See Acknowledgments on page 1377.
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https://doi.org/10.1016/j.bbmt.2018.01.035

score of <70 at third ASCT were unfavorable factors. A salvage third ASCT is of value for patients with relapsed myeloma, particularly for those with a long duration of response and chemosensitive disease at the time of transplantation.

INTRODUCTION

Autologous stem cell transplantation (ASCT) is a standard form of treatment for multiple myeloma (MM), especially for fit patients. It is performed either upfront as a first-line strategy or at first relapse [1]. Recent reports suggest that even in the era of new drugs, ASCT preferably should be performed upfront [2,3]. Upfront tandem ASCT, with the 2 transplantations performed within 6 months of each other, remains controversial [4-8].

At relapse, a second ASCT can also be a therapeutic option [9]. The prognosis of salvage ASCT is strongly associated with the duration of response after initial ASCT, with a threshold value ranging from 12 to 36 months [10-12]. A randomized prospective study in patients with a response duration of >12 months demonstrated longer progression-free survival (PFS) and overall survival (OS) in patients who received reinduction with bortezomib followed by salvage ASCT compared with a nontransplantation approach [13].

However, even after 2 ASCTs, either initial upfront tandem ASCT or 2 salvage ASCTs, the patients eventually relapse. In this setting, although a salvage third ASCT may be considered, outcomes of this approach have not been reported to date. Since the introduction of novel agents in salvage regimens, the prognosis of patients with relapsed MM has improved [14]. Therefore, a salvage third ASCT requires careful consideration regarding whether a survival benefit can be obtained at the expense of an additional toxicity risk. To address this issue, we analyzed the European Society for Blood and Marrow Transplantation (EBMT) data registry to assess the outcomes and prognostic factors for a salvage third autologous transplantation strategy in patients with relapsed MM.

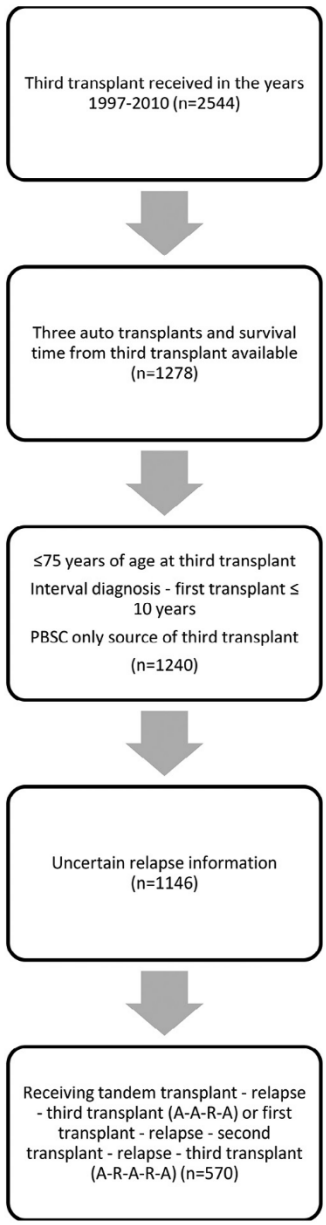
PATIENTS AND METHODS

Data Source

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Chronic Malignancies Working Party of the EBMT. There are no restrictions on centers for reporting data, except for those required by the law for patient consent, data confidentiality, and accuracy. Quality control measures include several independent systems, including confirmation of the validity of the entered data by the reporting teams, selective comparison of the survey data with minimum essential data-A (MED-A) datasets in the EBMT registry, cross-checking with the national registries, and regular in-house and external data audits. All patients whose transplantation data are reported to the EBMT by participating centers provide informed consent for use of the information for research purposes in an anonymous manner.

Patients

Between 1997 and 2010, 1146 patients with MM who had undergone at least 3 ASCTs and no allogeneic transplantations at the time of the third ASCT were registered in the EBMT database. Patients older than 75 years, those with an interval from diagnosis to first ASCT of >10 years, patients who received bone marrow transplants, those with an interval from relapse to ASCT of <1 month, and those with an uncertain relapse date were excluded from our analysis. Planned tandem ASCT was defined as 2 transplantations performed within a 6-month interval with at least 1 month between transplantations. The remaining study population comprised 596 patients (Consort flow diagram of patient selection). The high-dose regimen for the third transplant was defined as high-dose melphalan alone (140 or 200 mg/m^2). If melphalan was in combination with busulfan or bortezomib, or if the melphalan dose was different or unspecified or there was no melphalan use, it was classified as "other". Standard International Myeloma Working Group criteria were used to classify disease responses and define progression or relapse [15]. Relapsed myeloma after ASCT was defined as progressive disease or clinical relapse, requiring salvage therapy.



Statistical Analysis

The patient population was defined based on the known clinical parameters. Comparisons between groups were made using the chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney or Kruskal-Wallis test for continuous variables. All time-to-event endpoints were calculated from the day of the third transplantation and censored at the last available follow-up if the patient remained event-free. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. Relapse incidence and nonrelapse mortality (NRM) were calculated as competing risks using the proper nonparametric estimator and compared using the Gray test. The incidence of second primary malignancy (SPM) was also analyzed, with death as a competing event. OS was analyzed using a multivariable Cox model, checking for the proportionality of hazards by ap-

Table 1
Patient Characteristics at the Third ASCT in the AARA and ARARA Groups

Characteristic	AARA (n = 482)		ARARA (n = 88)	
Age, yr, median (range)	59	(29-74)		
Interval from second ASCT to first relapse, mo, median (range)	24	(<1-176)		
Interval from relapse to third ASCT, mo, median (range)	9	(1-122)		
Interval from second ASCT to first relapse, mo, n (%)				
0-18	173	(36)		
18-36	167	(35)		
>36	142	(29)		
Age, yr, median (range)			61	(35-72)
Interval from second ASCT to second relapse, mo, median (range)			11	(<1-114)
Interval from second relapse to third ASCT, mo, median (range)			11	(1-129)
Interval from second ASCT to second relapse, mo, n (%)				
0-6			22	(25)
6-18			39	(44)
>18			27	(31)
Hematologic status, n (%)				
CR	26	(6)	3	(4)
VGPR/PR	218	(48)	19	(22)
Stable disease/MR	55	(12)	10	(12)
Primary refractory/relapse/progression	159	(34)	53	(62)
KPS score, n (%)				
<70	30	(7)	6	(8)
≥70	373	(93)	70	(92)
High-dose regimen, n (%)				
Melphalan 200 mg/m^2	148	(31)	10	(12)
Melphalan 140 mg/m^2	18	(3)	8	(9)
Other*	177	(37)	32	(36)
Missing	139	(29)	38	(43)

* Other high-dose regimens: melphalan with bortezomib or busulfan or melphalan at another dose/unit area or unspecified or no melphalan.

plying methods based on scaled Schoenfeld residuals. The cutoff points for the time from the second transplantation to the last relapse were based on the literature, but the impact on the outcome of this factor as a continuous variable was checked, and the suitability of the cutoff points was confirmed by analysis of martingale residuals. Analyses were performed using SPSS version 23 (IBM, Armonk, NY) and R version 3.3.0 (R Institute for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

We could distinguish 2 main groups: 482 patients (81%) who underwent tandem ASCT and then a third ASCT after single relapse (AARA group) and 88 patients (15%) who underwent a first ASCT, a second ASCT after first relapse, and a third ASCT after second relapse (ARARA group). A third group, who received tandem ASCT after relapsing following single ASCT, comprised only 26 patients (4%) and was not studied.

MED-B data for the 570 patients included in the statistical analysis are presented for the following parameters at the third ASCT (Table 1): age, time from the second ASCT to relapse and time from relapse to the third ASCT, hematologic status, Karnofsky Performance Status (KPS), and type of high-dose regimen. The high-dose regimen (melphalan ≥140 mg/m^2) represented 19% of all regimen types before 2006 and 57% after 2006.

Table 2
Outcomes After Third ASCT in the AARA and ARARA Groups

Outcome	AARA (n = 482)		ARARA (n = 88)	
Engraftment, n (%)				
Primary graft failure	12	(3)	4	(5)
Engraftment/no failure	440	(96)	74	(95)
Secondary graft failure	4	(1)	0	(0)
Best response, n (%)				
CR	145	(34)	10	(12)
VGPR/PR	251	(59)	60	(74)
MR/stable disease	13	(3)	9	(11)
Relapse/progression	16	(4)	2	(3)
Causes of death, n (%)				
Relapse/progression	270	(84)	61	(84)
SPM	3	(1)	2	(3)
Other	50	(15)	10	(13)
Type of SPM, n (%)				
Acute leukemia	1	(6)	0	(0)
Lymphoma	0	(0)	1	(20)
Myelodysplasia	5	(29)	1	(20)
Solid tumor	11	(65)	3	(60)
Follow-up, mo, median (range)	61.6 (1-156)		48.5 (2.3-114)	

Similarly, Table 2 presents engraftment outcomes, best responses, causes of death and SPM, as well as follow-up data, after the third ASCT.

At diagnosis, the disease stage and myeloma isotype were not different between the AARA and ARARA groups (data not shown). Age at the third ASCT was similar in the 2 groups. There was no significant between-group difference in the KPS. More AARA patients achieved complete response (CR)/very good partial response (VGPR)/partial response (PR) before the third ASCT ($P < .001$), and more patients in this group received a high-dose melphalan (200 mg/m^2) regimen ($P < .001$). The time between the second ASCT and the last relapse was longer in the AARA group (24 months versus 11 months; $P < .001$). The time between the last relapse and the third ASCT was similar in the 2 groups (9 months versus 11 months; $P = .4$). The median duration of follow-up after the third ASCT was 61.6 months (range, 1 to 156 months) in the AARA group and 48 months (range, 2.3 to 114 months) in the ARARA group.

Outcomes after the Third Transplantation

In the AARA and ARARA groups, the median OS was 33 months and 15 months, respectively; the median PFS was 13 months and 8 months, respectively (Figure 1), and the 100-day NRM was 4% and 7%, respectively. Engraftment was similar in the 2 groups (96% and 95%; $P = .352$).The best response after the third ASCT was superior in the AARA group compared with the ARARA group: CR, 34% versus 12%; VGPR or PR, 59% versus 74%; minor response (MR) or stable disease (SD), 3% versus 11%; disease progression, 4% versus 3% ($P < .001$) (Table 2).

The cumulative incidence of relapse at 36 months was 68% (95% confidence interval [CI], 63% to 72%) in the AARA group and 75% (95% CI, 66% to 85%) in the ARARA group. The causes of death were relapse/progression (84% in the AARA group and 84% in the ARARA group), SPM (1% and 3%, respectively), and other causes (15% and 13%, respectively) (Table 2). The incidence of SPM after the third ASCT was 6% in the AARA group and 7% ARARA group, with a longer median time to SPM in the AARA group (43 months versus 12 months).

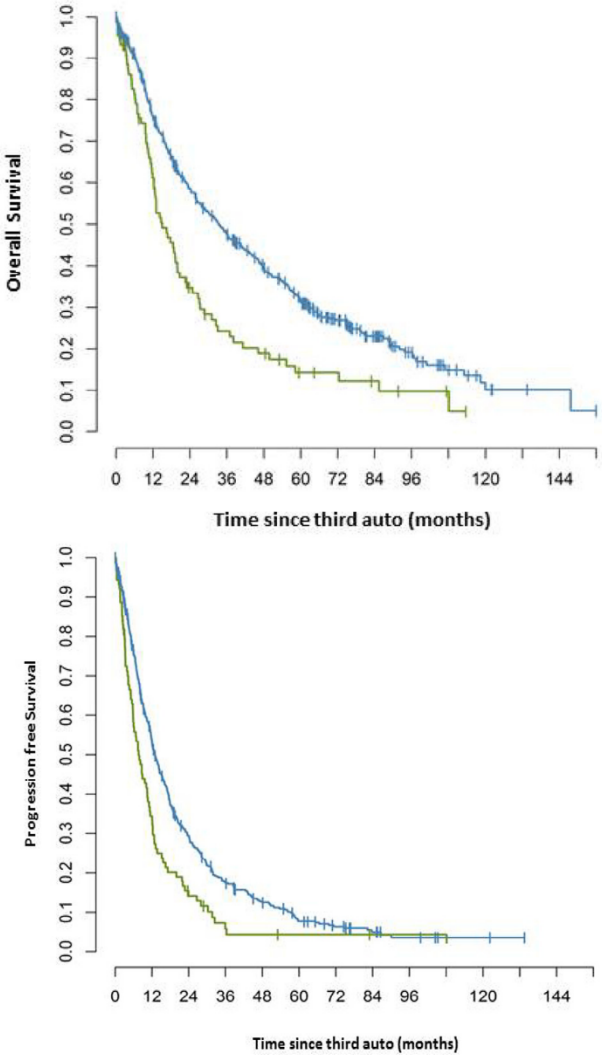


Figure 1. OS and PFS in the 2 subgroups: AARA (blue) and ARARA (green).

Survival as Related to the Duration of Remission after the Second ASCT

In both groups, the longer the duration of remission after the second ASCT, the better the outcome. In the AARA group, if relapse occurred within 18 months after tandem ASCT, the median OS was 17 months and the median PFS was 8 months; within 18 to 36 months, OS was 37 months and PFS was 14 months; and beyond 36 months, OS was 64 months and PFS was 24 months ($P < .001$ for both OS and PFS) (Figure 2A).

In the ARARA group, if relapse occurred within 6 months after 2 successive salvage ASCTs, the median OS was 7 months and the median PFS was 3 months; within 6 to 18 months, OS was 13 months and PFS was 7 months; and beyond 18 months, OS was 27 months and PFS was 12 months ($P < .001$ for OS and $P = .007$ for PFS) (Figure 2B).

Parameters Influencing Survival after Salvage Third Therapy

Univariate analysis

In a univariate analysis, the favorable prognostic factors for OS were a third ASCT performed in the most recent years, early stage of the disease at diagnosis, a longer time from the second ASCT to relapse, a better hematologic response at the third ASCT, a KPS of ≥70%, and a higher dose of melphalan. Sex, myeloma isotype, and the interval from diagnosis to first ASCT had no impact on OS (Table 3).

Multivariate analysis

In a multivariate analysis, only 1 factor was favorable: the time from second ASCT to relapse. If relapse occurred between 18 and 36 months compared to within 18 months, the HR was .62 (95% CI, .47 to .82; $P = .01$), and if it occurred after 36 months, the HR was .35 (95% CI, .25 to .49; $P < .001$). Two parameters were negative predictive factors: disease status at third ASCT (HR, 1.73; 95% CI, 1.33 to 2.24; $P < .001$) for relapse/progression versus other responses, and a KPS of <70% (HR, 2.48; 95% CI, 1.61 to 3.83; $P < .001$) (Table 4).

DISCUSSION

Despite the many advances in the treatment of MM, cure remains elusive, and patients typically require sequential regimens to control the disease for as long as possible. A second ASCT has been used by several groups in the management of recurrent MM; however, to our knowledge, this is the first report on salvage third ASCT.

The increased toxicity associated with repeated high-dose chemotherapy is a general concern, and a high frequency of grade 3 and 4 toxicities after salvage ASCT has been reported [16]. Although the safety of ASCT has improved in recent years, doubt may be raised regarding the use of a third ASCT as salvage therapy, given that this procedure is associated with increased toxicity and NRM. Nevertheless, after a second salvage ASCT, an NRM of 7% (95% CI, 3% to 13%) at 1 year and 12% (95% CI, 7% to 19%) at 5 years has been reported [10,17]. Thus, the survival benefit of salvage ASCT seems to outweigh the risks of adverse side effects in eligible patients. The present study indicates that a salvage third ASCT may still be beneficial with acceptable toxicity. In this study, the day +100 post-transplantation NRM was between 4% and 7% and the cumulative incidence of SPM was approximately 6%. Disease progression remained the leading cause of death.

According to our univariate analysis, survival has improved since 1997 and especially since 2009. We postulate that the improved OS in patients who underwent transplantation after 2009 is related to the use of novel agents in the treatment of relapse/progression before and/or after salvage ASCT [18]. The International Staging System score at diagnosis was also a highly significant prognostic factor, with a much shorter OS in patients with stage III disease. More than 80% of patients were still able to achieve a PR or better after a third ASCT; in a multivariate analysis, only patients whose disease had not progressed before ASCT benefited from transplantation.

Our observation that the time to progression after second ASCT was one of the most important factors predicting both PFS and OS is consistent with previous reports of salvage ASCT [16,17,19]. Other studies have found that the interval between transplantations is prognostic for OS, with a favorable outcome requiring an interval of at least 1 year between the first and second transplantations [17,19-22], although this finding was not confirmed in a smaller study [10]. A recent multivariate analysis of 55 patients undergoing salvage transplantation suggested that a duration of remission of >12 months after the first transplantation was predictive for both OS and PFS [11]. We confirm that a time threshold of 36 months is feasible for predicting outcome, as was reported in a Center for International Blood and Marrow Transplant Research study

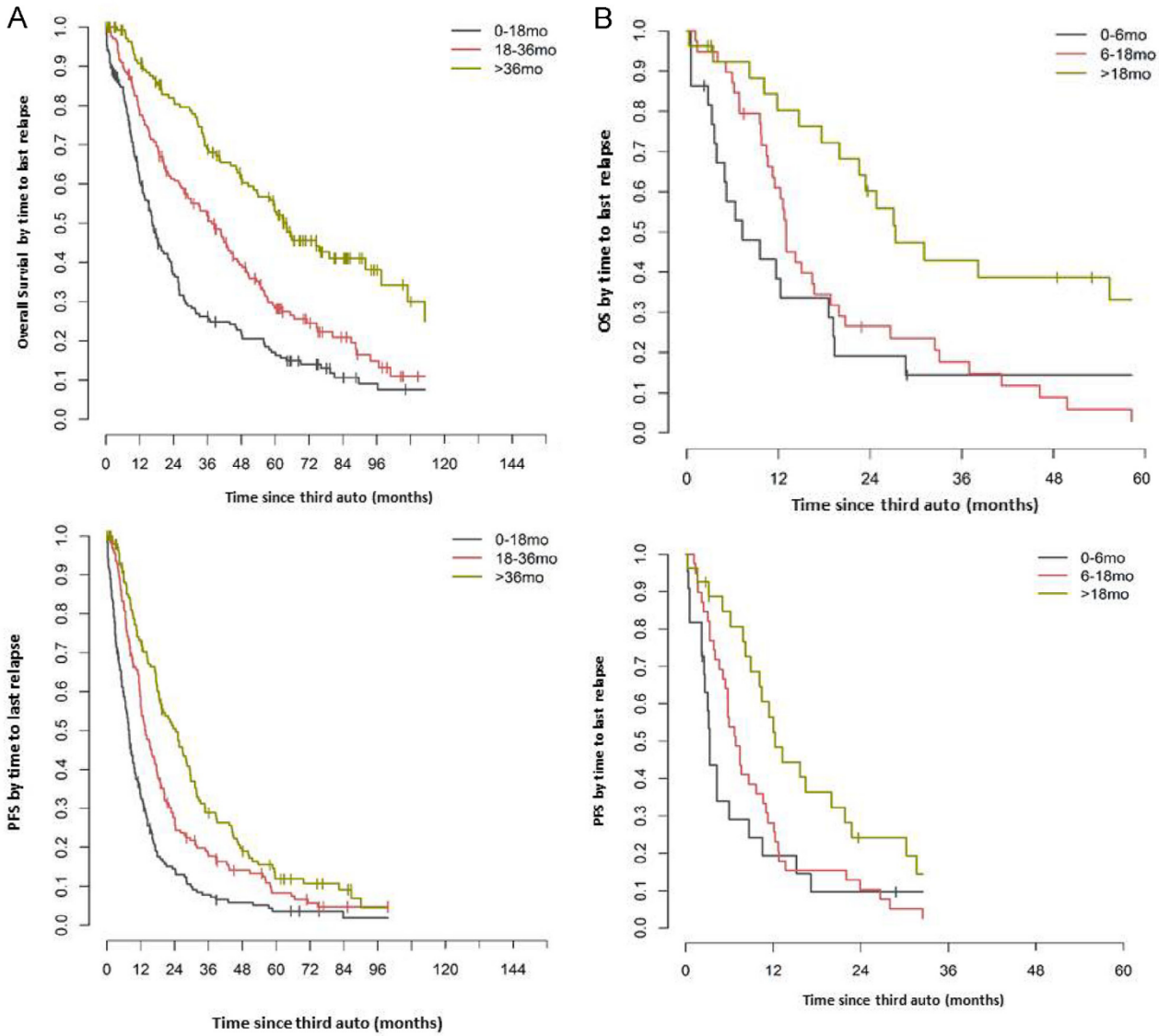


Figure 2. (A) OS and PFS according to the time from first relapse to third ASCT in the AARA group. (B) OS and PFS according to the interval from second relapse to third ASCT in the ARARA group.

examining first salvage ASCT post-ASCT [12]. In this analysis, patients with disease progression later than 36 months after first ASCT had a median OS after second ASCT of 49 months (95% CI, 34 to 108 months), compared with a median OS of 28 months (95% CI, 24% to 42%) in patients with a shorter progression-free interval after first ASCT. Other published retrospective studies have correlated better outcomes in patients who experienced relapse/progression more than 2 years after first ASCT [21]. As expected, in our study cohort, the threshold was much shorter for patients relapsing after 2 salvage ASCTs, with the disease becoming more resistant. The outcome was dismal in this setting if the patient relapsed within 6 months after the second ASCT, whereas beyond 18 months, the median OS was 27 months, which is encouraging in third-line treatment.

A consortium from the Nordic countries retrospectively studied the outcomes of second-line treatment in patients with MM who relapse after first-line ASCT [23]. Patients who underwent a second ASCT were compared with patients who were retreated with conventional cytotoxic drugs only or with regimens including novel drugs (proteasome inhibitors and/or immunomodulatory drugs) without a second ASCT. The median OS was 4.0 years for patients undergoing a second ASCT, compared with 3.3 years ($P < .001$) for those treated with novel drugs and 2.5 years ($P < .001$) for those receiving conventional cytotoxic drugs. A second ASCT also resulted in a significantly longer time to subsequent disease progression and a significantly longer time to the next treatment. The authors concluded that irrespective of the addition of novel drugs, patients with MM in first relapse after ASCT still appear to benefit from a second ASCT. A retrospective matched-pair analysis comparing a second transplantation and systemic chemotherapy gave similar results [24]. Thus, the benefit of salvage ASCT is still perceptible for eligible patients who have received novel therapies.

The present retrospective study has several limitations. First, it was not a prospective survey based on an intent-to-treat analysis, and we lacked precise data on how many

Table 3
Univariate Analysis of OS in the AARA Group

Variable	Median, mo	95% CI	Estimate, % at 36 mo	95% CI	*P* value
Period					.001
1997-2004	23	16-31	37	29-45	
2005-2008	34	26-46	48	40-55	
2009-2010	43	33-59	58	50-66	
Sex					.291
Male	32	26-37	46	40-51	
Female	38	26-47	51	43-59	
International Staging System stage					.031
I	48	21-76	57	40-73	
II	47	28-69	59	48-70	
III	32	26-37	45	39-51	
MM class					.919
IgG	36	29-47	50	44-57	
IgA	23	18-36	39	28-50	
Light chain	35	24-42	48	39-58	
Other Ig	35	24-43	49	40-58	
Nonsecretory	22	9-NA	44	20-69	
Interval from diagnosis to first ASCT					.378
0-6 mo	33	26-39	46	40-53	
6-12 mo	30	22-43	49	40-57	
1-10 yr	36	23-62	50	39-62	
Time from second ASCT to relapse					<.001
0-18 mo	17	13-20	26	19-33	
19-36 mo	38	26-45	52	44-60	
>36 mo	64	39-92	69	61-77	
Hematologic status					<.001
CR	80	19-NA	60	41-79	
VGPR/PR	47	36-55	60	53-66	
MR/stable disease	44	24-75	54	41-68	
Relapse/progression	18	14-24	29	22-37	
KPS					<.001
≥70	41	34-48	53	48-58	
<70	9	5-14	11	0-23	
Melphalan conditioning					.004
Melphalan 200 mg/m^2	56	41-62	65	57-73	
Melphalan 140 mg/m^2	41	9-NA	60	34-85	
Other	28	20-36	42	35-50	

patients were excluded from salvage ASCT owing to the presence of comorbidities, an insufficient quantity of stem cells, or progressive and/or refractory disease. This selection bias is the most important shortcoming. Second, the available database did not include MM-specific risk factors at relapse. Of note, the presence of cytogenetic abnormalities was not assessed in this study because of missing data in the majority of cases. Third, for many patients, information on the type of high-dose regimen was lacking, related to the fact that the data were collected only after the year 2006. We also did not know whether the autologous stem cells originated from a previously collected frozen sample or had been obtained after relapse. Finally, we had no information as to whether consolidation or maintenance therapy was given following transplantation. However, because our study focused on treatment provided between 1997 and 2010, very few patients——mostly those included in clinical trials——would have received such therapy, because this was not approved at the time.

Table 4
Multivariate Analysis of OS in the AARA Group

Variable	HR	95% CI	*P* value
Time to relapse (from second ASCT) versus baseline <18 mo			
18-36 mo	.62	.47-.82	.001
>36 mo	.35	.25-.49	<.001
Disease status at third ASCT			
Relapse/progression versus other	1.73	1.33-2.24	<.001
KPS score			
<70 versus ≥70	2.48	1.61-3.83	<.001

HR indicates hazard ratio.

In conclusion, a salvage third ASCT is feasible in patients with MM, with >80% of patients achieving at least a PR, although with increased NRM. This therapy is used mainly in 2 scenarios: tandem ASCT followed by relapse and a third ASCT, or, less commonly, a first ASCT followed by a first relapse, a second ASCT followed by a second relapse, and subsequently a third ASCT. The first scenario gives much better results, due in part to a better remission status at the third ASCT with no signs of increased SPM. In this group, if relapse occurred more than 3 years after the initial tandem ASCT, then the median OS after third ASCT was >5 years. The availability of novel agents may further improve the response to a third ASCT, rather than impairing its usefulness in the salvage setting, by enhancing the depth of response before ASCT, which could result in improved durability of the outcome.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

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