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ORIGINAL ARTICLE

Novel agent-based salvage autologous stem cell transplantation for relapsed multiple myeloma

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Abstract High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is a standard frontline therapy for multiple myeloma (MM). Therapeutic options for patients with relapsed MM after ASCT include novel agents in different combos, salvage ASCT (sASCT), and allogeneic transplant, with no unique standard of care. We retrospectively analyzed 66 MM patients who relapsed after up-front single or double ASCT(s) and received novel agent-based sASCT at five Italian centers. Median event-free survival from up-front ASCT(s) to first relapse (EFS1) was 44 months. Seventy-three percent of patients received sASCT at first disease progression. Re-induction regimens were bortezomib based in 87% of patients. Response to re-induction therapy included complete response (CR) 18%, ≥ very good partial response (VGPR) 48%, and overall response rate (ORR) 83%. Response to sASCT included CR 44%, ≥ VGPR 77%, and ORR 94%. With a median follow-up of 24 months after sASCT, 39 patients experienced disease progression. Median EFS from sASCT (EFS2) was 17 months. Median overall survival from ASCT (OS1) and sASCT (OS2) was 166 and 43 months, respectively. EFS2 and OS2 were significantly shorter in patients with EFS1 ≤ 24 months, in patients who did not receive sASCT at first disease progression and in patients with extramedullary disease (EMD). In multivariate analysis, EFS1 ≤ 24 months was associated with shorter EFS2 and OS2, EMD was associated with shorter EFS2, and < CR after sASCT was associated with shorter OS2. Novel agent-based sASCT is a safe and effective procedure for relapsed MM.

Keywords Multiple myeloma · Relapse · Salvage autologous stem cell transplantation · Novel agents · Outcomes

Introduction

The landscape of multiple myeloma (MM) has dramatically evolved over the last decade, with several new therapies and improved patient outcomes [1]. The first major change was the introduction of autologous stem cell transplantation (ASCT) in the late 1980s. Results of randomized trials comparing high-dose therapy (HDT) plus stem cell support with conventional chemotherapy have shown that ASCT improves progression-free (PFS) and overall (OS) survival [2, 3]. As a result, the procedure is regarded as the standard of care for patients with newly diagnosed MM aged up to 65–70 years, without substantial comorbidities [4, 5].

Novel agents such as thalidomide, bortezomib, lenalidomide, and, subsequently, second- and third-generation proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), incorporated into up-front ASCT as induction, consolidation, and maintenance therapy, have further improved rates of response and survival [6–8].

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However, despite these highly effective therapies, almost all MM patients will eventually relapse. At the time of disease recurrence, no standard salvage approach is clearly defined. Many therapeutic options are available, including retreatment with prior effective therapy, novel or experimental agents, and, in selected cases, allogeneic transplant [9]. More recently, anti-SLAMF7 and anti-CD38 monoclonal antibodies have been approved for the treatment of relapsed MM [10]. IMiDs and PIs are currently the backbone for novel very effective triplet combinations [11–15].

The use of ASCT at relapse (salvage ASCT, sASCT) is an appealing option [16, 17]. In contrast to the up-front setting, in which the role of HDT and ASCT is well established, sASCT has been investigated mainly in retrospective, registry-based, or single-center studies. A review of these studies showed an overall response rate of 64.3% (95% CI 27.3–97.4%), with a median PFS of 12 months and a median OS of 32 months [18]. Furthermore, the overall transplant-related mortality (TRM) is less than 5%. A phase 2 study and a phase 3 study have been recently published, both demonstrating the benefit of sASCT preceded by a novel agent-based re-induction therapy [19, 20].

The aim of the present study was to retrospectively analyze the outcome, in terms of response rate, event-free survival (EFS), and OS, of 66 MM patients treated at relapse, after up-front single or tandem ASCT(s), with novel agents incorporated into sASCT, and to identify prognostic factors associated with prolonged survival.

Materials and methods

Patients

Between January 2005 and December 2014, 66 patients at five Italian institutions underwent sASCT after up-front single or double ASCT(s). In all cases, sASCT was preceded by a novel agent-based re-induction therapy.

Definitions

A transplant was defined as salvage if the patient had already received at least one prior ASCT and underwent a further ASCT after evidence of disease progression, regardless of the number of lines of treatment administered after up-front ASCT(s).

EFS1 was defined as the interval between up-front ASCT(s) and first relapse/progression. EFS2 was defined as the interval between sASCT and subsequent relapse or death. OS1 was defined as the interval between up-front ASCT(s) and death from any cause. OS2 was defined as the interval between sASCT and death or last follow-up.

Response

Response criteria were those established by the International Myeloma Working Group (IMWG) [21]. Response to up-front and salvage ASCT(s) was evaluated at 3 months post transplantation. Response to re-induction therapy was assessed on the first day of each cycle and within 30 days after the end of re-induction therapy.

Toxicity and adverse events

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3. TRM was assessed from day + 1 to day + 100 after sASCT.

Statistical analysis

The statistical analysis was performed using the StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP. Descriptive statistics, as arithmetic mean and standard deviation or median with the interquartile range as indicated, were calculated for continuous variables. For qualitative variables, absolute frequencies and percentages have been provided. Summary statistics were presented according to the re-induction treatment and the 95% confidence intervals if variables were subjected to statistical inference. Treatment response was assessed between groups using the $\chi 2$ test or Fisher's exact test as appropriate. The Kaplan-Meier method was used for survival analyses to estimate survival outcomes. The log-rank test was adopted to compare survival curves. Multivariable analysis, using the semi-parametric Cox proportional hazard regression model, was performed to assess factors affecting negatively to EFS2 and OS2. Regarding the safety analysis, stacked bar chart was adopted to present toxicity results to evaluate the more recurrent adverse event and its grade according to NCI-CTC. All tests were considered significant with p values less than 0.05.

Results

Patient characteristics

Patient characteristics at the time of sASCT are listed in Table 1. In total, 66 MM patients, of whom 36 men and 30 women, who relapsed after up-front single (67%) or tandem (33%) ASCT(s), received a sASCT. Median age at sASCT was 60 (IQR, 57–66) years. Induction therapy in preparation to up-front ASCT consisted in conventional chemotherapy with vincristine-adriamycin-dexamethasone (VAD) in 35% of patients, bortezomib-based regimens in 24% of patients (11 patients received bortezomib-thalidomide-dexamethasone, VTD, and 5 patients received bortezomib-

Table 1 Patient Characteristics at sASCT

No. of patients	66
Male/female	36/30
Age: median (IQR)	60 (57–66) years
ISS stage:	
I	31 (47%)
II	13 (20%)
III	4 (6%)
unknown	18 (27%)
Isotype:	
IgG	38 (58%)
IgA	10 (15%)
BJ	16 (24%)
Non secretory myeloma	2 (3%)
BM PC: median (IQR)	27.5 (10–60)%
Extramedullary disease	3/63 (5%)
No. of lines before sASCT:	
1	48 (73%)
≥ 2	18 (27%)
Re-induction regimens	
bortezomib-based:	57 (87%)
VTD	*58%*
VCD	*4%*
PAD	*6%*
VD	*19%*
non-bortezomib-based:	9 (13%)
Rd	*8%*
TD	*5%*

ISS international staging system, *BJ* Bence Jones, *BM PC* bone marrow plasma cells, *sASCT* salvage autologous stem cell transplantation, *VTD* bortezomib-thalidomide-dexamethasone, *VCD* bortezomib-cyclophosphamide-dexamethasone, *PAD* bortezomib-doxorubicin-dexamethasone, *VD* bortezomib-dexamethasone, *Rd* lenalidomide-dexamethasone, *TD* thalidomide-dexamethasone

dexamethasone, VD), and IMiDs-based combinations in 41% of patients (26 patients treated with thalidomide-dexamethasone, TD, and 1 patient treated with cyclophosphamide-thalidomide-dexamethasone, CTD). None received maintenance after up-front ASCT(s). The best response to up-front ASCT(s) included complete response (CR) 43%, ≥ very good partial response (VGPR) 75%, overall response rate (ORR: ≥ partial response, PR) 99%. Median EFS1 was 44 (IQR, 35–61) months and median time from up-front ASCT(s) to sASCT was 59 (IQR, 46–81) months. Seventy-three percent of patients received sASCT at first disease progression. Cytogenetic (FISH) analysis after disease recurrence and before sASCT was available only in a third of patients and showed the presence, either isolated or co-segregated, of t(4;14) in 17% of patients and del(17p) in 13% of patients. Extramedullary disease (EMD) was detected in 3 out of 63 evaluable patients. Re-induction regimens before sASCT were bortezomib based in 87% of patients (see Table 1 for details). Twenty-three patients received 2 cycles of consolidation therapy after sASCT, with VTD, VD, and lenalidomide-dexamethasone (Rd) used in 16, 5, and 2 patients, respectively. None received maintenance after sASCT.

Sixty-four percent of patients already had harvested stem cells for sASCT, while 24 patients needed further peripheral blood stem cell (PBSC) mobilization, 5 patients after single and 19 patients after double up-front ASCT(s). The majority of them (42%) received granulocyte colony-stimulating factor (G-CSF) plus plerixafor as a re-mobilization regimen; cyclophosphamide at the dose of 4 g/m^2 plus G-CSF alone or in combination with plerixafor in case of CD34+ < 20/μl and G-CSF alone were used in 7, 6, and 1 patients, respectively. Overall, the median number of re-collected PBSC was 3.5 (IQR 2.5–4.1) × 10^6 CD34+/kg. High-dose melphalan (HDM) was the standard conditioning regimen before sASCT; a full dose of 200 mg/m^2 was administered to 32 patients, whereas reduced doses of 140 and 100 mg/m^2 were used in 11 and 2 patients, respectively, due to the presence of older age and/or renal impairment and/or comorbidities. The median number of PBSC infused was 3.8 (IQR, 2.9–4.9) × 10^6/kg. Neutrophils (≥ 500/mmc) and platelets (≥ 20.000/mmc) engraftment occurred at 11 (IQR, 10–12) and 12 (IQR, 11–14) days post transplantation, respectively.

Response

Response to re-induction therapy was of high quality (≥ VGPR) in 48% of patients, with a CR rate of 18%. The ORR of the entire cohort was 83%. The ORR was higher and the median time to response was shorter with bortezomib-based in comparison to non-bortezomib-based regimens, also adjusting for the treatment received as first line (ORR 88% versus 60%, $P = 0.049$; median time to response 2 versus 4 months, $P = 0.01$, respectively). Seventy-seven percent of patients reached at least a VGPR as their best response to sASCT, with a CR rate of 44%. Twenty-six percent of patients upgraded from less than CR before sASCT to CR after sASCT ($P < 0.0001$) (Table 2). The number of patients receiving consolidation was too small to see any impact on either response or survival outcomes.

Toxicity

sASCT-related toxicities are illustrated in Fig. 1. The rate of grade 3–4 adverse events was 55%; they were all manageable, with only two patients who died within 100 days from sASCT, owing to cardiac events, accounting for 3% TRM. Gastrointestinal adverse events were the most frequent, as they were observed in 48% of patients (grade 1–2, 30%; grade 3–4, 18%). Grade 3–4 mucositis was seen only in two patients. Twenty-three patients experienced a febrile episode;

Table 2 Response to re-induction therapy and best response to sASCT

Response to re-induction therapy	Total	Bortezomib-based	Non-bortezomib-based	*P* value
CR	18%	20%	10%	ns
≥ VGPR	48%	55%	20%	0.044
ORR (≥ PR)	83%	88%	60%	0.049
Best response to sASCT	Total	Bortezomib-based	Non-bortezomib-based	*P* value
CR	44%	49%	20%	ns
≥ VGPR	77%	83%	50%	0.035
ORR (≥ PR)	94%	96%	80%	ns

CR complete response, *VGPR* very good partial response, *ORR* overall response rate, *PR* partial response, *sASCT* salvage autologous stem cell transplantation, *ns* not statistically significant

fever of unknown origin (FUO), sepsis with identification of the pathogen, and lung invasive fungal infection (IFI) were detected in 12, 8, and 3 patients, respectively. Other adverse events included six cardiac toxicities (such as atrial fibrillation, heart failure, ischemic heart disease) and two CVC-related deep vein thrombosis.

The toxicity profile of VTD, the more frequent re-induction regimen applied before sASCT, was superimposable to that reported in the literature. Peripheral neuropathy grade 3–4 occurred in 15% of patients and thromboembolic events (deep vein thrombosis/pulmonary embolism) grade 3–4 occurred in 4% of patients.

Survival outcomes

With a median follow-up of 24 months after sASCT, the median EFS2 was 17 months. EFS2 was significantly shorter in patients with EFS1 ≤ 24 months (10 versus 18 months, respectively, $P = 0.003$), in patients who did not receive sASCT at first disease progression (10 versus 18 months, $P = 0.03$), in patients with EMD (10 versus 18 months, $P = 0.008$) and in patients who received re-induction therapy with a non-bortezomib-based regimen (10 versus 18 months, $P = 0.01$), also adjusting for the treatment received as first line.

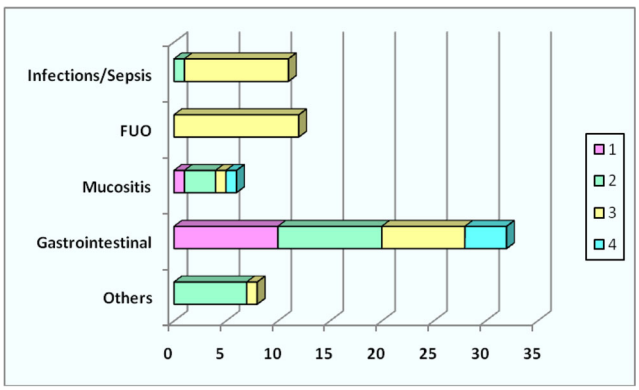


Fig. 1 sASCT-related toxicity. 1, grade 1; 2, grade 2; 3, grade 3; 4, grade 4; FUO, fever of unknown origin

Median OS1 and OS2 were 166 and 43 months, respectively. Twenty-three patients died after sASCT, 74% of them due to disease progression. OS2 was significantly shorter in patients with EFS1 ≤ 24 months (14 versus 58 months, $P = 0.003$), in patients who did not receive sASCT at first disease progression (14 versus 58 months, $P = 0.008$), in patients with EMD (14 versus 58 months, $P = 0.03$) and in patients who failed CR after sASCT (30 months versus not reached, $P = 0.006$).

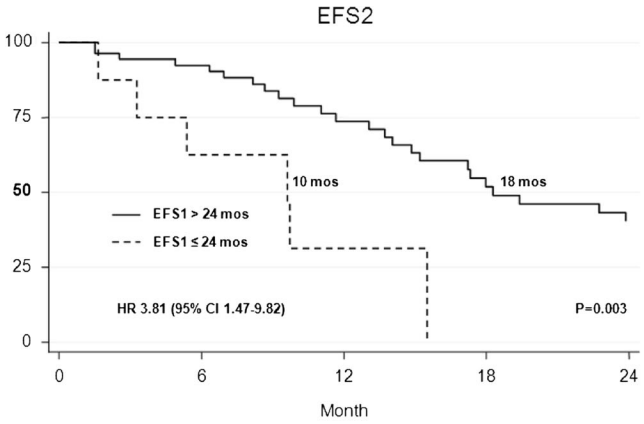
Figures 2 and 3 illustrate survival outcomes according to EFS1 and to the number of previous lines of therapy, respectively.

As previously mentioned, cytogenetics at the time of sASCT was available in a minority of patients, thus preventing any analysis of its impact on clinical outcomes.

In multivariate analysis (Table 3), the duration of EFS1 significantly influenced both EFS2 and OS2 (EFS1 ≤ 24 months: HR 4.78, 95% CI 1.77–12.91, for EFS2, and HR 3.81, 95% CI 1.26–11.5, for OS2). The presence of EMD was associated with a shorter EFS2 (HR 6.57, 95% CI 1.78–24.19). As in the up-front setting, the quality of response to sASCT correlated with outcome, with patients achieving less than CR who experienced a shorter OS2 (HR 3.73, 95% CI 1.24–11.19).

Discussion

HDT followed by ASCT is currently considered the standard of care for young newly diagnosed MM patients. Two large phase 3 randomized studies have recently demonstrated that up-front ASCT still continues to be the reference treatment for fit patients with newly diagnosed MM, even in the novel agent era [22, 23]. Further improvement in the treatment of MM has derived from the complementary use of novel agents [4]. However, despite many advances observed in the last years, a cure for MM is still elusive and patients will eventually relapse after frontline therapy. Optimal treatment at relapse has not been standardized; several different novel agents, in



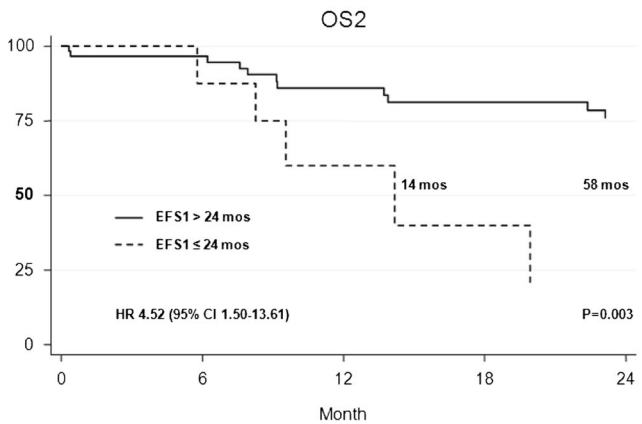
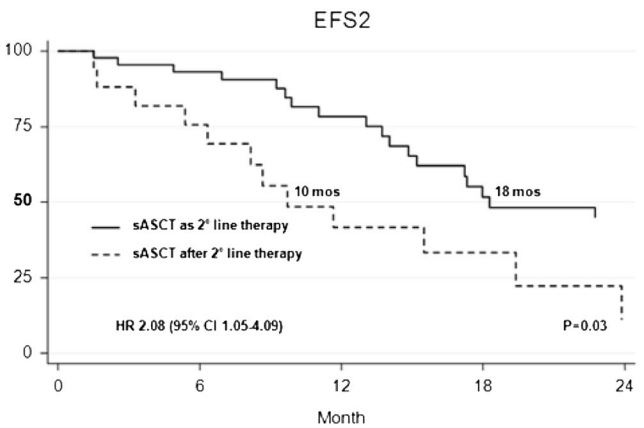


Fig. 2 Outcomes after sASCT according to EFS1. EFS2 event-free survival 2, defined as the interval between sASCT and relapse or death; EFS1 event-free survival 1, defined as the interval between up-front ASCT(s) and first relapse/progression; OS2 overall survival 2, defined as the interval between sASCT and death or last follow up; mos months

different combos, or sASCT constitute available options [9, 24].

Since the very first report by Tricot and colleagues, the role of sASCT has been investigated in many retrospective studies [25]. Chemosensitivity and remission duration after the first transplant were identified as the most relevant prognostic factors for long-term disease control after sASCT. In addition, the number of prior lines of therapy had a significant impact on patient outcomes and many investigators suggested that sASCT should be used at first disease progression [18]. Almost all studies underlined the prognostic role of time to progression (TTP) after the first transplant, with cut-offs between a *minimum* of 6 and a *maximum* of 36 months. In multivariate analyses, patients relapsing ≥ 18 and/or 24 and/or 36 months after up-front ASCT had superior PFS and OS after sASCT [26–37]. Several reports showed that the larger the number of prior therapies was, the shorter was the OS after sASCT; as a consequence, sASCT should be considered an integral component of initial salvage strategies [32, 33]. Lastly, the depth of response after re-induction treatment and after sASCT was found to be another important prognostic factor [28, 36–39].

Only one multicenter randomized phase 3 study investigating the role of sASCT has been published so far [20]. One hundred seventy-four MM patients at first relapse, progressed ≥18 months after a previous ASCT, were treated with bortezomib-doxorubicin-dexamethasone (PAD), and then randomized to HDM and sASCT or cyclophosphamide (400 mg/m^2/week for 12 weeks). After a median follow-up of 31 months, median PFS was significantly longer in the sASCT arm than in the cyclophosphamide arm (19 versus 11 months, $P < 0.0001$, respectively), whereas OS did not significantly differ between the two groups. The long-term follow-up (52 months) analysis demonstrated an advantage in terms of OS in the sASCT cohort (67 versus 52 months, $P = 0.022$, respectively) [40]. Notably, the standard chemotherapy arm was sub-optimal if compared to novel approved triplet combinations. The Nordic Myeloma Study Group has reported the results of a prospective non-randomized phase 2 study, in which 53 bortezomib-naive MM patients were



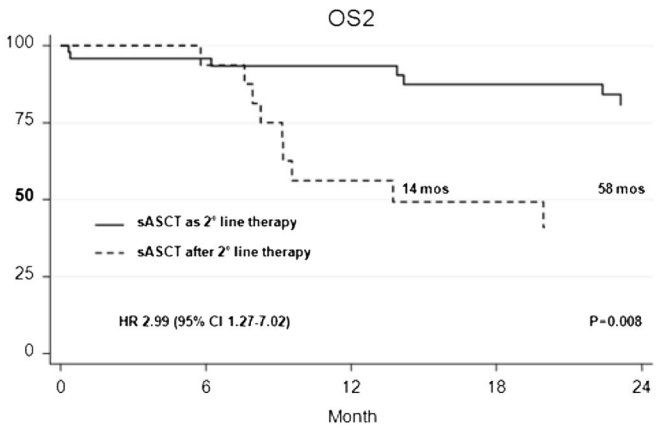


Fig. 3 Outcomes after sASCT according to previous lines of therapy. EFS2 event-free survival 2, defined as the interval between sASCT and relapse or death; OS2 overall survival 2, defined as the interval between sASCT and death or last follow-up; sASCT salvage autologous stem cell transplantation; mos months

Table 3 Multivariate analysis of factors negatively influencing EFS2 and OS2

Variable	Hazard ratio	95% CI	*P* value
EFS2			
EFS1 ≤ 24 months	4.78	1.77–12.91	0.002
EMD	6.57	1.78–24.19	0.005
OS2			
EFS1 ≤ 24 months	3.81	1.26–11.50	0.018
< CR after sASCT	3.73	1.24–11.19	0.019

sASCT salvage autologous stem cell transplantation; *EFS2* event-free survival 2, defined as the interval between sASCT and relapse or death; EFS1, event-free survival 1, defined as the interval between up-front ASCT(s) and first relapse/progression; *OS2* overall survival 2, defined as the interval between sASCT and death or last follow up; *CI* confidence interval; *EMD* extramedullary disease; *CR* complete response

treated at first relapse with bortezomib-dexamethasone as re-induction and bortezomib plus HDM as conditioning regimen to sASCT. Median PFS and median OS from the start of re-induction therapy were 21.6 and 46.6 months, respectively [19].

On the basis of the results of aforementioned retrospective and prospective studies, the American Society for Blood and Marrow Transplantation stated a grade B recommendation for the use of sASCT in the relapse setting, as the procedure was judged safe and efficacious in prolonging PFS [16]. It is recommended that the *minimum* length of TTP after initial ASCT should be ≥ 12 months to consider sASCT (grade D recommendation). Similar conclusions were drawn by the IMWG in the consensus guidelines for the optimal use of sASCT [17]. The procedure is strongly recommended in case of initial remission duration longer than 18 months.

We have retrospectively examined a homogeneous cohort of MM patients treated at relapse with a novel agent-based re-induction therapy, followed by sASCT. Re-induction regimens were bortezomib based in 87% of patients, VTD and VD being the most used. Responses to re-induction therapy were of high quality (≥ VGPR) in 48 % of patients, with a CR rate of 18%. sASCT allowed a further improvement in the response rate, with 77% of patients reaching at least a VGPR and 44% of patients being in CR. Twenty-six percent of patients upgraded from less than CR before sASCT to CR after sASCT ($P < 0.0001$). With a median follow-up of 24 months after sASCT, the median EFS2 and OS2 were 17 and 43 months, respectively. Responses and survival outcomes were of note, similar to or even better than those reported in many retrospective studies. According to others, we found that disease remission duration after initial ASCT, number of prior lines of therapy, and response to sASCT were significantly associated with outcome. In fact, EFS2 and OS2 were longer in patients with EFS1 > 24 months, in patients who received sASCT at first disease progression and in patients without evidence of EMD. In multivariate analysis, EFS1 significantly influenced both EFS2 and OS2; EMD and CR after sASCT correlated with EFS2 and OS2, respectively. Despite EMD being detected only in three patients, it was associated with a very poor outcome.

Most groups found the frequency and intensity of toxicities following sASCT to be similar. Taking into account all retrospective studies, the median TRM was 4.1% [18]. Our data confirmed that sASCT is feasible and safe. Thanks to the use of plerixafor, PBSC re-mobilization and collection were successful in 24 patients. The 3% TRM was similar to that observed in the up-front setting.

Salvage therapy for MM has been revolutionized by the availability of novel agents. Several studies demonstrated the efficacy of thalidomide, bortezomib, and lenalidomide in the relapse/refractory setting [9]. The use of bortezomib, single agent or in combination with dexamethasone, led to a median PFS ranging between 6 and 11 months, and a median OS ranging between 16 and 30 months. Equally, median PFS and median OS for patients treated with lenalidomide, alone or plus dexamethasone, ranged between 5 and 13 months, and between 23 and 38 months, respectively. Responses and survival outcomes were superior when these agents were used as second-line therapy [41–46]. Garderet et al. demonstrated the superior efficacy of a novel agent-based triplet combination, VTD, over TD, in patients relapsing after ASCT [47]. Median PFS was significantly longer for patients treated with VTD (18.3 versus 13.6 months, $P = 0.001$, respectively) and a trend towards improved OS was observed.

Newer triplet combinations including second-generation PIs and monoclonal antibodies were recently compared to doublets, in randomized phase 3 trials, enrolling MM patients relapsed after one to three prior treatments (ASPIRE, TOURMALINE-MM1, ELOQUENT-2) or after at least one previous therapy (CASTOR, POLLUX). In all studies, triplets resulted in better PFS and CR rate than doublets. Median PFS was 26.3 versus 17.6 months ($P = 0.0001$), 20.6 versus 14.7 months ($P = 0.01$), and 19.4 versus 14.9 months ($P < 0.001$), in the carfilzomib-lenalidomide-dexamethasone, ixazomib-lenalidomide-dexamethasone, and elotuzumab-lenalidomide-dexamethasone groups versus the control group, respectively [11–13]. Daratumumab, the first in class anti-CD38 monoclonal antibody, has been evaluated in two phase 3 randomized trials [14, 15]. The CASTOR trial and the POLLUX trial demonstrated the superiority of the daratumumab arm over the control arm in terms of median PFS (not reached versus 7.2 months, $P < 0.001$, and not reached versus 18.4 months, $P < 0.001$, respectively), CR rate, and achievement of minimal residual disease (MRD) negativity (7.2% versus 1.6%, $P = 0.0017$, and 22.4% versus 4.6%, $P < 0.000001$, respectively) [14, 15, 48–50].

Because published results on the use of sASCT are derived from studies done before the availability of newer anti-

myeloma agents and combos, prospective randomized trials are urgently needed to reconsider the role of sASCT compared to best non-ASCT therapy, such as second-/third-generation IMiDs and PIs, monoclonal antibodies and check-point inhibitors, and to delineate the true potential for sASCT in the relapsed disease. In the up-front setting, ASCT demonstrated to significantly improve the outcomes also in the era of first- and second-generation novel agents. Whether the incorporation of sASCT in a triplet regimen used as induction before and consolidation/maintenance after transplant may improve patient outcome will be defined in such designed prospective randomized trials.

In summary, our study had the capacity of clearly identifying prognostic factors associated with better outcome after sASCT. Patients who benefit the most from this procedure are those in the first relapse, with EFS1 > 24 months and achieving CR after sASCT. The limitations of our analysis are the small sample size distributed over almost 10 years and the lack of cytogenetic data.

To conclude, despite the development of very active therapies for MM, patients eventually relapse. At the time of disease recurrence, no standard salvage approach is clearly defined. sASCT is an option that has been associated with high response rate and prolonged PFS. Optimal use of sASCT needs to be explored in prospective randomized clinical trials that integrate novel triplet combinations at different phases of the ASCT procedure (induction, consolidation, and maintenance). In the meantime, as demonstrated in our analysis, sASCT should be considered a valid clinical option for the treatment of relapsed MM.

Compliance with ethical standards

Conflict of interest Michele Cavo has received honoraria and has been a member of the advisory board for Celgene, Janssen, Amgen, Takeda and Bristol-Myers Squibb. Elena Zamagni has received honoraria from Janssen-Cilag, Celgene and Amgen. All other authors declare to have no relevant financial interests in competing.

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