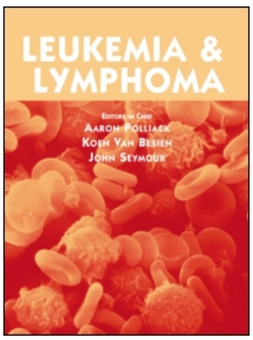

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ORIGINAL ARTICLE

Primary refractory multiple myeloma: a real-world experience with 85 cases

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ABSTRACT

This study determined whether 85 patients with multiple myeloma (MM) double-refractory to primary induction therapy with triplet regimens had a homogenous prognosis. The overall response rate (ORR) after the second-line therapy was 51%. Patients who proceeded to immediate autologous stem cell transplantation (ASCT) had better ORR than those who received conventional therapies (62% vs. 31%). The ORR for patients who had ASCT directly after the frontline therapy was higher than for those treated with other regimens as the second line therapy (91% vs. 45%) and offered ASCT as the third-line therapy (91% vs. 55%). The median progression-free survival (PFS) after the second-line therapy and median overall survival were 21.6 months and 35.6 months, respectively. ASCT after the second line treatment (HR = 0.24) was an independent predictor of PFS. Eligible patients with primary refractory MM achieve the most benefit from ASCT, also performed immediately after first line induction therapy.

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Double-refractory multiple myeloma; prognosis; treatment response; survival

Introduction

Multiple myeloma (MM) represents approximately 1% of all malignancies and accounts for about 10% of hematological neoplasms [1, 2], which makes it the second most frequent disease in the latter group. Implementation of new therapeutic options, proteasome inhibitors (PIs), immunomodulatory agents (IMIDs) and monoclonal antibodies, have revolutionized the treatment of MM. A real-world study conducted in 2006–14 demonstrated that the novel agents were administered as an induction regimen in 61.3% of MM patients on average, as compared with 8.7% in 2006 [3], and the 2-year survival after treatment with the new drugs was shown to be 1.25-fold higher than in 2006 [3]. Also, the overall response rates (ORRs; at least partial response) to triplet induction treatment with PIs plus IMiDs are generally reported in the 80–90% range [4–9]. Unfortunately, the proportion of patients with primary double-refractory MM (resistant to PIs and IMIDs) is estimated at 10–20% [5, 7], and prognosis in these cases is inferior compared with those who responded to induction treatment [10–13].

Observations from a few studies suggest that patients who do not respond to induction therapy (e.g. due to primary double- or triple-refractory MM) are not a homogeneous population in terms of prognosis, and some of them might benefit from an

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appropriately selected second line treatment and/or ASCT. Triple-refractory multiple myeloma was defined as failure to respond to treatment with at least one immunomodulatory drug (IMiD), one proteasome inhibitor and one anti-CD38. This may, at least partially, circumvent the poor prognosis associated with the failure of primary induction therapies, thus, contributing to a better survival [14]. Furthermore, some studies demonstrated that administration of additional lines of therapy prior to ASCT in patients who did not respond adequately to the first-line treatment might not be associated with a survival benefit [15, 16] and, whenever eligible, such patients might proceed to transplant without further attempts to achieve a deeper response [14]. Nevertheless, no consensus has yet been reached with regards to further management of non-responders [17–19].

The aim of this real-life multicenter study was to verify whether patients with primary double-refractory MM are homogenous in terms of unfavorable prognosis and to determine the optimal available second-line treatment options which lead to better outcomes in this group.

Methods

Case selection

Between October 2005 and January 2018, patients with a newly diagnosed MM refractory to induction therapy with IMIDs and/or PIs were identified from the medical records at 17 participating institutions in Argentina, Czechia, Hungary, Italy, Poland, Spain, Hong Kong and United States. The patients were eligible for the analysis if they did not achieve at least a partial response (PR) [20] after at least four cycles of induction with an immunomodulator and proteasome inhibitor-containing triplet regimen (VTD: bortezomib, thalidomide, dexamethasone, or VRD: bortezomib, lenalidomide, dexamethasone). Patients with smoldering myeloma, amyloidosis and/or primary plasma cell leukemia were excluded from the analysis. The study protocol was reviewed and approved by the Institutional Review Board of each participating institution.

Data analysis

Patient demographics were abstracted from the medical records of participants fulfilling the inclusion criteria. The list of analyzed parameters included: age at diagnosis of MM, sex, heavy and light chain isotype, R-ISS [21], presence of FISH cytogenetic abnormalities included in the R-ISS [21]: t(14;16), t(4;14), TP53 and/or del17p, hemoglobin level, serum concentrations of calcium, albumin, beta-2 microglobulin (B2M), and lactate dehydrogenase (LDH; elevated vs. normal), estimated glomerular filtration rate (eGFR), radiographic evidence of lytic lesions, degree of bone marrow involvement (%), type of frontline therapy, therapeutic responses to the second-line treatment, progression-free survival (PFS) and overall survival (OS). Treatment outcomes were classified by the International Myeloma Working Group, as complete response (CR), stringent complete remission (sCR), very good partial response (VGPR), partial response (PR), stable disease (SD) and progressive disease (PD) [20]. Overall response rate (ORR), i.e. the proportion of all responses $\geq$ PR, was also calculated. OS was defined as the time from the response to the second-line therapy to last follow-up or death, and PFS as the time from the response to the second-line therapy to the date of progression, relapse or death from any cause. The patients known to be alive or respectively without progression at last follow-up or status unknown at last follow up were censored for OS and PFS analysis.

Statistical analysis

The *Chi*-square test was used to compare categorical variables. For the survival analysis, the Kaplan–Meier method was used to generate survival curves, which were then compared using the log-rank test. The Cox proportional-hazard regression method was used to fit univariate and multivariate survival models, the results of which are reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Variables with >50% of missing data were not included in the survival analyses. All reported *p*-values are two-sided and were considered significant if less than .05. Calculations and graphics were obtained using the statistical software Stata version 16.1 (StataCorp LLC, College Station, TX, USA).

Results

A total of 85 patients with an established diagnosis of MM with less than a partial response to the induction treatment were included in the analysis. The median age at the time of MM diagnosis was 58 years (range 28–80). The study group included 51% of male patients. Information about the R-ISS [21] was available in 57/85 (67%) patients; this group included 14/57 (25%), 31/57 (54%) and 12/57 (21%) patients with R-ISS I, R-ISS II and R-ISS III MM, respectively. Information about the MM isotype was available in all

(97%) patients; the proportions of patients with IgG and non-IgG isotypes were 60% (51/85) and 40% (34/85), respectively. High-risk cytogenetic abnormalities were found in 18/69 (26%) patients with available cytogenetic data. Other clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics of 85 patients with primary double-refractory multiple myeloma.

Characteristic	Number (%) or median (range)
Age at myeloma diagnosis, years	58 (28–80)
Age ≥60 years	37/85 (43%)
Male sex	43/85 (51%)
Monoclonal protein subtype	
Heavy chain isotype	
IgG	51/85 (60%)
IgA	11/85 (13%)
IgM	2/85 (2%)
Biclonal	2/85 (2%)
Light chain only	19/85 (23%)
Light chain isotype	
Kappa	31/85 (36%)
Lambda	22/85 (26%)
Hemoglobin, g/dl	10.2 (3.5–15.3)
Estimated GFR, ml/min	67.0 (3.0–105.0)
Serum calcium level, mg/dl	9.7 (8.0–17.6)
Lytic lesions	46/57 (81%)
Serum albumin level, g/l	32.8 (2.5–55.0)
Serum beta-2-microglobulin level, mg/dl	3.9 (1.3–32.3)
Increased serum LDH level	29/67 (43%)
Bone marrow involvement (%)	55.0 (6.4–100.0)
R-ISS stage	
Stage I	14/57 (25%)
Stage II	31/57 (54%)
Stage III	12/57 (21%)
High-risk cytogenetics	18/69 (26%)
Induction therapy	
VTD	52/85 (61%)
VRD	33/85 (39%)

The study patients received the induction therapy with novel agents, VTD (52/85, 61%) or VRD (33/85, 39%). The proportion of patients who received novel agents, IMIDs and/or PIs, within the framework of the salvage treatment was 76% (65/85); the remaining patients were administered conventional chemotherapy (6/85), monoclonal antibodies (3/85), or proceeded to ASCT directly after the failed induction (11/85). Another 42/85 patients (49%) underwent ASCT following the salvage treatment (Table 2).

The ORR after the second-line therapy was 51%. Patients who underwent ASCT as consolidation had significantly better ORR than those who did not (62% vs. 31%, $p = .001$). The ORR for patients who proceeded to ASCT directly after the frontline therapy was higher than for those treated with other regimens within the framework of the salvage treatment (91% vs. 45%, $p = .004$). Patients who underwent ASCT directly after the primary induction failure also had higher ORR than those in whom ASCT was carried out after the second line treatment (91% vs. 55%, $p = .028$) (Table 2).

The median PFS after the second-line therapy was 21.6 months (95% CI 8.0–39.2) (Figure 1(a)). Univariate Cox analysis identified ASCT as consolidation and VRD induction as the only significant predictors of PFS (Table 3). Multivariate Cox analysis demonstrated that

Table 2. Treatment responses in 85 patients with primary double-refractory multiple myeloma who received the second-line therapy and were evaluable for response.

Group	CR	sCR	VGPR	PR	SD	PD	ORR	*p*-Value (ORR)
Overall	2 (2%)	3 (3%)	16 (19%)	22 (26%)	28 (33%)	14 (16%)	43 (51%)	
By second-line treatment*								
IMIDs (n = 21)	0 (0%)	1 (5%)	3 (14%)	6 (29%)	4 (19%)	7 (33%)	10 (48%)	.052
PIs (n = 24)	0 (0%)	1 (4%)	4 (17%)	5 (21%)	10 (42%)	4 (17%)	10 (42%)	
IMIDs + PIs (n = 20)	0 (0%)	0 (0%)	6 (30%)	5 (25%)	6 (30%)	3 (15%)	11 (55%)	
ChT (n = 6)	0 (0%)	0 (0%)	1 (17%)	1 (17%)	4 (67%)	0 (0%)	2 (33%)	
Others (n = 3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)	0 (0%)	
Only ASCT (n = 11)	2 (18%)	1 (9%)	2 (18%)	5 (45%)	1 (9%)	0 (0%)	10 (91%)	
ASCT with/without salvage therapy (vs. salvage therapy only)								
yes (n = 53)	2 (4%)	1 (2%)	14 (26%)	16 (30%)	18 (34%)	2 (4%)	33 (62%)	.001
no (n = 32)	0 (0%)	2 (6%)	2 (6%)	6 (19%)	10 (31%)	12 (37%)	10 (31%)	
ASCT without the salvage therapy (vs. salvage therapy with/without ASCT)								
yes (n = 11)	2 (18%)	1 (9%)	2 (18%)	5 (45%)	1 (9%)	0 (0%)	10 (91%)	.004
no (n = 74)	0 (0%)	2 (3%)	14 (19%)	17 (23%)	27 (36%)	14 (19%)	33 (45%)	
ASCT without the salvage therapy (vs. ASCT after the salvage therapy)								
yes (n = 11)	2 (18%)	1 (9%)	2 (18%)	5 (45%)	1 (9%)	0 (0%)	10 (91%)	.028
no (n = 42)	0 (0%)	0 (0%)	12 (29%)	11 (26%)	17 (40%)	2 (5%)	23 (55%)	

*__IMIDs__: bendamustine + lenalidomide + dexamethasone, pomalidomide + dexamethasone, lenalidomide, lenalidomide + prednisone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, thalidomide + dexamethasone; __PIs__: carfilzomib + cyclophosphamide + dexamethasone, carfilzomib + dexamethasone, melphalan + prednisone + bortezomib, bortezomib + doxorubicin + dexamethasone, bortezomib + cyclophosphamide + dexamethasone, bortezomib + dexamethasone, bortezomib + dexamethasone + venetoclax, bortezomib + dexamethasone + cyclophosphamide + etoposide + cisplatin; __IMIDs + PIs__: carfilzomib + lenalidomide + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide; bortezomib + dexamethasone + thalidomide + cisplatin + doxorubicin + cyclophosphamide + etoposide, carfilzomib + pomalidomide + dexamethasone, ixazomib + lenalidomide + dexamethasone, ixazomib + lenalidomide, bortezomib + lenalidomide + dexamethasone, bortezomib + lenalidomide + dexamethasone + bendamustine, bortezomib + lenalidomide + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide, bortezomib + dexamethasone + thalidomide + doxorubicin + prednisone; __ChT__: cyclophosphamide, dexamethasone + cyclophosphamide + etoposide + cisplatin, etoposide + dexamethasone + cytarabine + cisplatin, vincristine + carmustine + cyclophosphamide + melphalan + prednisone/vincristine + carmustine + doxorubicin + prednisone, vincristine + doxorubicin + dexamethasone; __Others__: daratumumab, daratumumab + pomalidomide + dexamethasone.

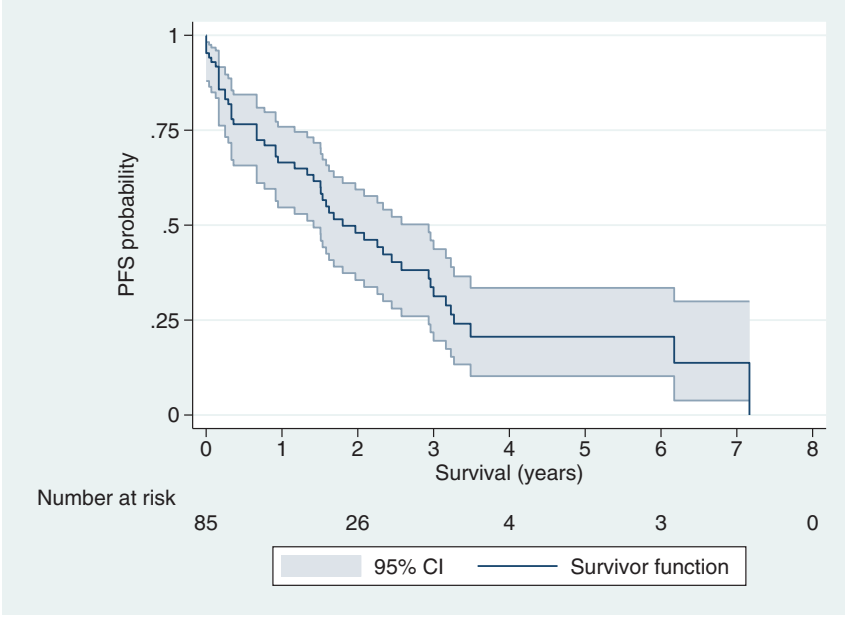

Figure 1. Progression-free survival estimates in 85 treated patients with primary double-refractory multiple myeloma for the entire cohort (a) and stratified by inclusion of ASCT after the failed induction (b).

Table 3. Univariate and multivariate analyses for progression-free survival in 85 patients with primary double-refractory multiple myeloma who received the second-line therapy.

	Univariate analysis		Multivariate analysis	
Predictor (fraction of patients)	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (years)	1.01 (0.98–1.03)	.657	1.00 (0.97–1.03)	.996
Age >60 years (37/85)	1.34 (0.76–2.35)	.428		
Female sex (42/85)	1.32 (0.76–2.31)	.419		
IgG (51/85)	0.69 (0.38–1.23)	.103		
Hemoglobin <10 g/dl (35/79)	0.86 (0.48–1.54)	.605		
Estimated GFR <60 ml/min (17/49)	1.71 (0.78–3.73)	.177		
Serum calcium >9.65 mg/dl (38/71)	1.16 (0.63–2.16)	.632		
Lytic lesions (46/57)	1.45 (0.60–3.52)	.523		
Serum albumin <33 g/l (38/74)	0.63 (0.34–1.18)	.153		
Serum B2M ≥5.5 mg/dl (22/66)	1.76 (0.92–3.36)	.087		
Increased serum LDH level (29/67)	1.58 (0.81–3.11)	.180		
High-risk cytogenetics (18/69)	1.51 (0.73–3.12)	.267		
R-ISS stage II/III (43/57)	1.58 (0.71–3.50)	.260		
R-ISS stage III (12/57)	1.23 (0.50–2.99)	.652		
Bone marrow involvement >50% (27/54)	1.91 (0.94–3.88)	.074		
VRD induction (33/85)	0.38 (0.21–0.70)	.002	0.49 (0.25–0.98)	.045
Novel agents in the 2nd line (65/85)	0.63 (0.27–1.52)	.307		
ASCT (53/85)	0.26 (0.15–0.48)	<.001	0.32 (0.16–0.65)	.001
ASCT without salvage treatment (11/85)	0.51 (0.19–1.36)	.182		

ASCT as consolidation (HR = 0.24, 95% CI 0.13–0.45, $p < .001$) was independent predictor of PFS regardless of the type of induction and patient age. The median PFS in patients who underwent ASCT was 30.9 months (95% CI 17.0–74.1) versus 4.0 months (95% CI 2.0–20.2) in those who did not receive ASCT (log-rank $p < .001$, Figure 1(b)).

The median follow-up was 44.6 months (95% CI 18.1–76.6), with a median OS of 35.6 months (95% CI 11.8–119.6) (Figure 2(a)). Univariate Cox analysis identified age >60 years, IgG isotype, eGFR <60 ml/min, serum B2M ≥5.5 mg/dl, increased serum LDH level and ASCT as consolidation as significant predictors of OS (Table 4). None of these factors was identified as an independent predictor of OS on multivariate Cox analysis. The predictive value of ASCT as consolidation was at a threshold of statistical significance (HR = 0.37, 95% CI 0.12–1.13, $p = .081$) when included in the multivariate model. The median OS in patients who underwent ASCT was 46.4 months (95% CI 24.6–119.6) versus 11.0 months (95% CI 2.6; not reached) in those who did not receive ASCT (log-rank $p = .002$) (Figure 2(b).

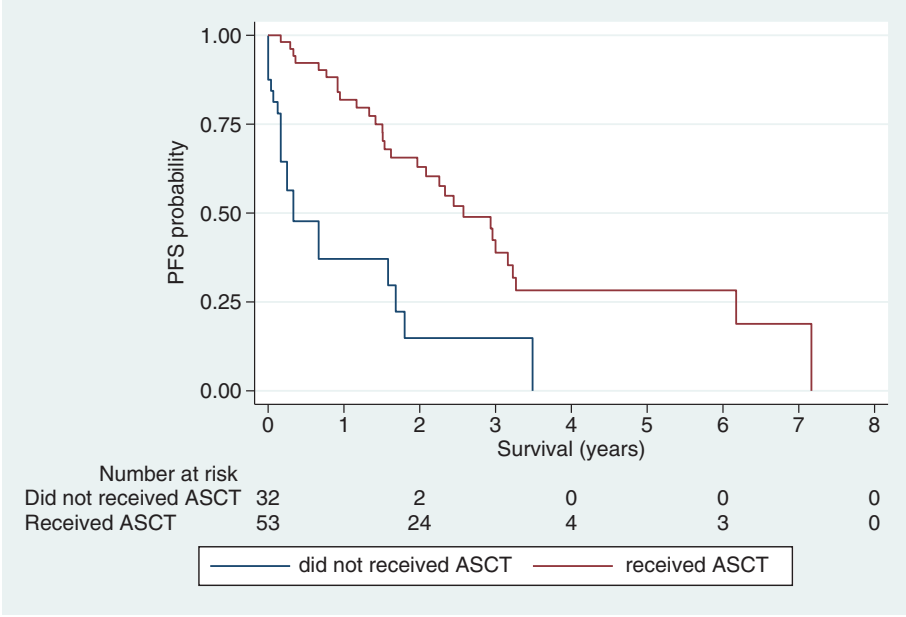

Figure 2. Overall survival estimates in 85 treated patients with primary double-refractory multiple myeloma for the entire cohort (a) and stratified by inclusion of ASCT after the failed induction (b).

Table 4. Univariate and multivariate analyses for overall survival in 85 patients with primary double-refractory multiple myeloma who received the second-line therapy.

	Univariate analysis		Multivariate analysis	
Predictor (fraction of patients)	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age >60 years (37/85)	2.54 (1.29–4.99)	.007	2.09 (0.79–5.55)	.140
Female sex (42/85)	1.22 (0.64–2.31)	.540		
IgG (51/85)	0.49 (0.25–0.95)	.035	0.41 (0.11–1.52)	.184
Hemoglobin <10 g/dl (35/79)	1.03 (0.53–2.02)	.927		
Estimated GFR <60 ml/min (17/49)	3.35 (1.48–7.60)	.004	0.98 (0.14–7.01)	.983
Serum calcium >9.65 mg/dl (38/71)	1.18 (0.59–2.34)	.644		
Lytic lesions (46/57)	2.16 (0.65–7.15)	.209		
Serum albumin <33 g/l (38/74)	0.87 (0.45–1.71)	.695		
Serum B2M ≥5.5 mg/dl (22/66)	2.43 (1.21–4.90)	.013	1.62 (0.28–9.47)	.592
Increased serum LDH level (29/67)	2.62 (1.27–5.41)	.009	1.99 (0.69–5.74)	.204
High-risk cytogenetics (18/69)	1.85 (0.84–4.06)	.126		
R-ISS stage II/III (43/57)	1.46 (0.59–3.66)	.414		
R-ISS stage III (12/57)	1.66 (0.65–4.22)	.286		
Bone marrow involvement >50% (27/54)	1.48 (0.69–3.14)	.310		
VRD induction (33/85)	0.71 (0.37–1.38)	.317		
Novel agents in the 2nd line (65/85)	1.08 (0.38–3.09)	.878		
ASCT (53/85)	0.33 (0.17–0.63)	.001	0.37 (0.12–1.13)	.081
ASCT without salvage treatment (11/85)	0.18 (0.02–1.37)	.099		

Discussion

Treatment of primary refractory MM constitutes a serious challenge and the outcomes in patients with primary induction failure are suboptimal. Double-refractory MM, non-responding to PIs and IMIDs, is considered a particularly aggressive form of the disease and no consensus approach to management of patients with this entity have been proposed thus far [19]. The aim of this real-life multicenter study was to determine whether patients with primary double-refractory MM are homogenous in terms of unfavorable prognosis and if implementation of ASCT immediately after failing triplet induction might contribute to better outcomes in this group.

To summarize, this study demonstrated that approximately half of the patients with primary double-refractory MM responded to the second-line treatment. The proportions of the responders were significantly higher among patients who underwent ASCT as consolidation, especially those who proceeded to ASCT directly after the induction therapy, without a salvage treatment. However, also up to 30% of transplant ineligible patients responded to the second therapy after the failed induction. The median

PFS after the second-line therapy was 21.6 months, with a median OS of 35.6 months. ASCT was identified as an independent predictor of improved PFS but was not associated with a statistically significant OS benefit, probably due to the availability of later line salvage therapies.

The treatment outcomes documented in this study are better than in previous reports on patients with primary refractory MM. In one study, PFS and OS in patients with MM refractory to novel regimens (most often bortezomib-based) were 4.7 months and 11.6 months, respectively [22]. According to Gertz et al. [23], patients who did not respond to IMIDs prior to ASCT consolidation had PFS of 13.1 months and OS of 30.4 months. In another study, median PFS and OS in double-refractory MM were 14.4 months and 38.9 months, respectively [14]. Probably, the better outcomes in our series might be explained by a relatively large proportion of patients eligible for ASCT, 56% versus 19–20% in the previous studies [14, 23]. It is also worth mentioning here that later generation PIs (i.e. carfilzomib), IMiDs (pomalidomide) and anti-CD38 antibodies may be efficacious salvage options in these primary refractory patients but the majority of this cohort examined predates their availability.

Indeed, ASCT turned out to be a significant predictor of a better response to the second-line treatment and an independent predictor of PFS in our patients. Importantly, better treatment responses were also observed in patients who proceeded to ASCT directly after the induction therapy, without a salvage treatment. ASCT without a salvage therapy was not identified as a significant predictor of PFS; perhaps the lack of statistical significance on Cox analysis was associated with a very small proportion of patients who were qualified for ASCT directly after the failed induction therapy (11/85, 13%). Published evidence suggests that ASCT could be the best currently available treatment option for patients with primary double-refractory MM. According to literature, post-ASCT ORRs in patients with refractory MM approximated 60–90% [14, 24–28], and hence, were similar to the overall response rates documented in our present study (62% for ASCT overall, 91% for ASCT without a salvage therapy). Considering all the above, proceeding to ASCT directly in patients with primary induction failure seems to be a recommended approach, especially given that other salvage therapy options in MM refractory to novel agents are generally limited [19].

According to literature, independent unfavorable predictors of survival in refractory MM include older age, worse performance status, extramedullary disease, advanced ISS, elevated LDH and adverse cytogenetics [10, 14, 29–31]. Some of those factors were also identified as significant predictors of OS in our present study. Similar to Cohen *et al.* [10], we did not demonstrate a significant effect of adverse cytogenetics, an established unfavorable prognostic factor in MM [32, 33], but this might be associated with the substantial proportion of missing cytogenetic data in our series (slightly below 20%).

ASCT was not independently associated with the OS but this is almost certainly due to other potential salvage regimens. However, considering its significant beneficial effect on PFS, we recommend ASCT as the first option for transplant eligible patients with primary refractory MM, at least until some of unique anti-MM therapies with various mechanisms of action that are currently in clinical trials proven effective. This concept is supported also by other retrospective studies reported in the literature [10, 34, 35].

Limitations

While the homogeneity of our group in terms of induction therapies is a strength of this real-life study, we are also aware of potential limitations. The study group was recruited over a long period of time, between 2005 and 2018, which made it heterogeneous in terms of the salvage treatments, and thus, the outcomes. Hence, the subgroup analysis comparing responses to specific regimens is predictably underpowered and might be biased due to the occurrence of Will Rogers phenomenon. Further, the proportion of patients who proceeded to ASCT directly after the failed induction might be too small for meaningful conclusions. Furthermore, some clinical data were missing. It also needs to be stressed that while the ORRs in this series were relatively high, the proportions of CRs, sCRs and VGPRs were relatively lower, which might raise a question about the depth of the response. The higher ORR and PFS benefit shown with transplant vs non-transplant salvage therapies, supports the recommendation favoring second-line ASCT in primary double-refractory myeloma patients. However, it is assumed the number of patients who received second-line carfilzomib, pomalidomide, and daratumumab-based salvage therapies in this cohort is small. Both transplant-eligible and ineligible patients now receive these therapies in second-line which are not yet known to be inferior to second-line ASCT in this setting. Randomized studies would be needed to answer this question.

Conclusions

Patients with primary double-refractory MM are not a homogenous group in terms of unfavorable prognosis. Eligible patients who did not respond adequately to the frontline therapy with novel agents may achieve the maximal benefit from immediate ASCT, although transplant following the second line therapy also is associated with improved outcomes compared with no transplant. Finally, up to 30% of transplant ineligible patients may respond to the second therapy after the failed induction.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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