original article

Outcomes of autologous stem cell transplantation for multiple myeloma in Saudi Arabia

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BACKGROUND: In 2015, multiple myeloma (MM) represented 1% of all cancers and about 5% of hematologic malignancies in Saudi cancer registry. We conducted this large study because only small pilot studies have examined MM outcomes after autologous stem-cell transplantation (ASCT). The standard therapy for eligible patients is induction chemotherapy followed by ASCT.

OBJECTIVES: Determine the demographic characteristics of MM patients and the outcomes of ASCT.

DESIGN: Retrospective.

SETTING: Tumor registry database of major tertiary cancer care center in Riyadh.

PATIENTS AND METHODS: We identified patients with newly diagnosed MM who underwent ASCT from October 1997 to March 2015.

MAIN OUTCOME MEASURES: The demographic characteristics of MM patients and the outcomes of ASCT in the form of response evaluation, progression-free survival (PFS) and overall survival (OS).

SAMPLE SIZE: 169 patients with newly diagnosed MM.

RESULTS: The median age at diagnosis was 51 years (range 23–69) and 100 (59.2%) were male. The most common immunoglobulin (Ig) subtype was IgG-kappa (80 patients; 47.6%). Most patients presented with advanced ISS stage III (75 patients; 47.5%). The cytogenetic analysis was documented in only 87 patients (51.4%); about half (48.3%) had normal cytogenetics by fluorescence in situ hybridization. Deletion 13 was present in 18.4% of patients. In post-induction therapy, 84 patients (50%) achieved a complete response, which increased to 78.1% (132 patients) after ASCT. The median PFS and OS post-transplantation were 30 and 202 months, respectively. Only one patient (<1%) died in the first 100 days after transplantation.

CONCLUSIONS: Our transplant eligible MM patients tend to be younger with a higher OS and a low ASCT-related mortality (<1%) than is reported internationally.

LIMITATIONS: Usual limitations of a retrospective analysis using registry-level data; no data on quality of life.

CONFLICT OF INTEREST: None.

Multiple myeloma (MM) is a heterogeneous disease of genetically distinct subtypes characterized by abnormal clonal proliferation of the plasma cells in the bone marrow, leading to end-organ damage in the form of renal impairment, lytic bony lesions, hypercalcemia and anemia.[1] MM represents 1-2% of all cancers and around 10-17% of all hematologic malignancies.[2,3] According to the Saudi Cancer Registry report from 2015, MM represented 1% of all cancers and about 5% of hematologic malignancies.[4]

Historically, the vincristine-doxorubicin-dexamethasone (VAD) regimen was used as induction chemotherapy before autologous stem cell transplantation (ASCT). Since the introduction of novel agents and the proven efficacy and tolerability of these agents, VAD is currently not considered a preferred induction regimen in MM. In the era of conventional chemotherapy, a meta-analysis of nine trials confirmed the efficacy of ASCT after induction chemotherapy in the degree of response and event-free survival, with three trials showing better overall survival.[5] In the last decade, with the advent of the novel agents such as immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, and ixazomib) and monoclonal antibodies (elotuzumab and daratumumab), the role of upfront ASCT has become controversial in certain subgroups and needs further studies to be evaluated; however, it is still widely recommended for eligible patients.[6] Despite all these advances, MM still an incurable disease which eventually relapses and needs subsequent lines of treatment.[7] We conducted this retrospective analysis to study the demographic characteristics of MM patients and the outcomes of ASCT in Saudi Arabia. To our knowledge, this is the first large study to report MM outcomes after ASCT from Saudi Arabia.

PATIENTS AND METHODS

We collected data from the tumor registry database of King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh. Newly diagnosed MM patients who underwent ASCT in our center between October 1997 and March 2015 were eligible for data analysis. The diagnosis of MM was confirmed based on the International Myeloma Working Group criteria (IMWG).[8] Staging was by the International Staging System (ISS) for multiple myeloma. Other plasma cell dyscrasias including monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma were excluded. This study was approved by the institutional review board of KFSHRC. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Endpoints were the outcomes of ASCT in newly diagnosed MM in terms of overall survival (OS), progression-free survival (PFS), mortality at 100 days after transplantation as well as identification of the demographics and prognostic factors in the Saudi population. The sequence of therapy in our protocol was similar to the international standard of care using induction followed by hematopoietic cell mobilization, high-dose chemotherapy and ASCT. Our standard induction therapy was the vincristine-doxorubicin-dexamethasone (VAD) regimen until 2010. A total of 28.4% of patients in our cohort received VAD as induction. In 2010, we integrated novel agents in induction. The three main combinations that were used included thalidomide/dexamethasone, bortezomib/thalidomide/dexamethasone and cyclophosphamide/ bortezomib/dexamethasone (VCD). Our mobilization protocol consisted of cyclophosphamide 1.5 gm/m^2 and G-CSF 5 µg/kg q12h. The product was then cryopreserved and infused on day zero after conditioning with standard melphalan 200 mg/m^2.

Patient characteristics are summarized using frequencies for categorical variables and medians with ranges for continuous variables. Probabilities for OS and PFS were calculated using the Kaplan–Meier estimator. Survival curves were compared using the log-rank test. Our endpoints were response rate after induction, OS and PFS. OS was defined as survival from the time of diagnosis to the date of death or last follow-up, while PFS was calculated from the time of transplantation to disease progression. Univariate and multivariate analysis were done using Cox regression hazard model with corresponding 95% confidence intervals. Statistical analysis was carried out using IBM SPSS version 20.

RESULTS

The median age of the 169 patients with newly diagnosed MM who underwent ASCT was 51 years (range 23–69 years); 100 were male (59.2%). The most common immunoglobulin (Ig) subtype was IgG kappa (80 patients; 47.6%) (**Table 1**). The second most common Ig subtype was the light chain (32 patients; 19%). Most patients presented with advanced ISS stage III (75 patients; 47.5%). Cytogenetic analysis data were available for 87 patients only (51.4%), and about half of these (48.3%) had normal cytogenetics by fluorescence in-situ hybridization (FISH). The most common genetic abnormality was deletion 13 (18.4%). Forty-eight patients (28.4%) received the VAD regimen; and 42 patients (24.9%) received the VCD regimen. Maintenance therapy post-

ASCT (in the form of interferon, thalidomide or lenalidomide) was used in only 17.8% of patients.

Outcome and survival

After induction therapy, 84 patients (50%) achieved complete response (CR) or better (using IMWG 2014 response criteria).[9] CR rate improved after ASCT to 78.1% (132 patients). There was no significant impact of ISS staging on the pre- or post-transplantation response with a *P* value of .49 and .45, respectively. Only one patient died in the first 100-days post-transplantation due to ovarian cancer. The median PFS and OS post-transplantation for the whole cohort was 30 and 202 months, respectively (**Figures 1 and 2**).

Univariate and multivariate analysis using Cox regression for associated variables and survival (PFS and OS) are shown in **Tables 2a, 2b, 3a and 3b**. Only pre-transplant response showed a statistically significant influence on PFS. The hazard ratio (HR) of those who achieved partial response compared to those who achieved stringent CR was 3.88 (*P*=<.001 and .01 by univariate and multivariate analysis, respectively). Only the cytogenetic abnormalities showed a significant impact on OS, where the deletion of chromosome 13 was associated with the worst prognosis with HR 6.22 and 7.87 and *P* value <.001 and <.001 on univariate and multivariate analysis, respectively. Interestingly, 89 patients (52.7%) who were transplanted after 2010 showed a statistically significant poor OS by multivariate analysis with HR 4.45 (*P*=.04) as compared with those who were transplanted before 2010, despite advances in novel therapy use and supportive care.

DISCUSSION

The low proportion of MM from the total hematologic malignancies pool in the Saudi population is probably multifactorial. First, the majority (72%) of the Saudi population is between 15 and 65 years of age;[10,11] while MM is typically a disease of the elderly. The median age in our cohort was 51 years, lower than the 66-70 years reported in the international data,[11] although this difference can be explained by selection bias. We only included patients who underwent ASCT, but the median age was still below the international median age of 57 years reported in transplant MM patients.[7] The median age of two previous small pilot studies in Saudi Arabia was 60 and 65 years, but those cohorts were not restricted to transplant patients.[12,13] Second, referral bias to KFSHRC (a tertiary care facility), and under-reporting probably contributed to the lower representation of MM as a part of the hematologic malignancies.

The most commonly involved Ig was IgG kappa (47.6%), whereas light chain myeloma accounted for 19% of our patients, which is comparable to what was reported in the Mayo Clinic series (34% and 16%, respectively).[14] Almost half of the patients presented with advanced stage, ISS stage III (47.5%), which is probably related to diagnostic and referral delays. There was no significant impact of ISS staging on the pre- or post-transplantation response rate. The cytogenetic analysis data were available for only 87 patients (51.4%); about half had normal cytogenetics on presentation (48.3%). We used FISH to identify cytogenetics because we had some difficulties in karyotyping results and some were unavailable; also the low yield of karyotype in MM (around 50% of cases) is well known and many important aberrations may be cryptic.[14] The most common genetic abnormality was deletion 13 (18.4%), which showed a

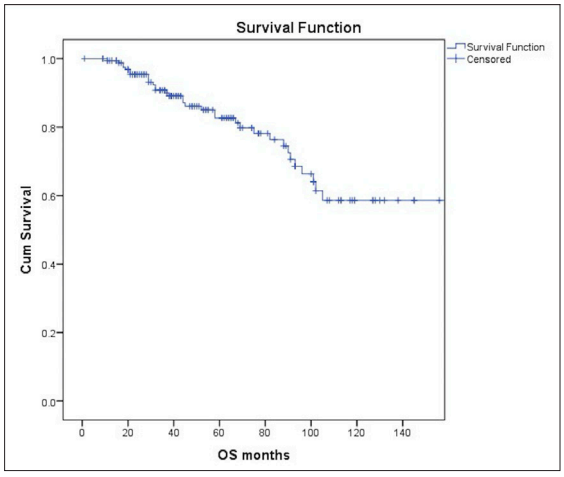

Figure 1. Overall survival of the 169 patients.

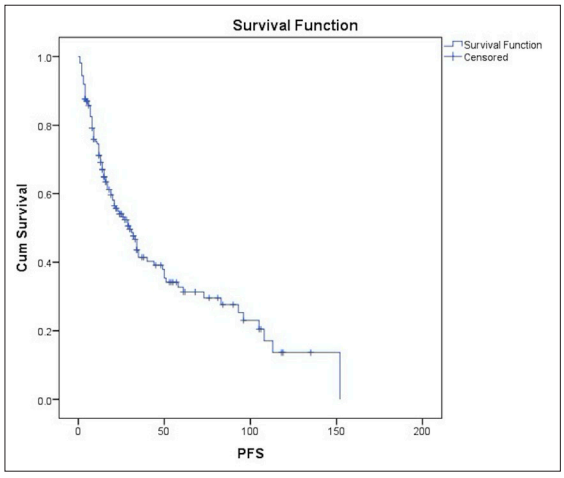

Figure 2. Progression-free survival of the 169 patients.

Table 1. Clinical characteristics of 169 newly diagnosed patients with multiple myeloma who underwent autologous stem cell transplantation.

Variable	
Immunoglobulin subtype	
IgG kappa	80 (47.6)
IgG lambda	24 (14.2)
IgA kappa	14 (8.3)
IgA lambda	8 (4.8)
IgM kappa	1 (0.6)
IgD	1 (0.6)
Light chain	32 (19)
Non secretory	8 (4.8)
ISS stage	
I	44 (27.8)
II	39 (24.7)
III	75 (47.5)
Cytogenetic by FISH	
Normal	42 (48.3)
Del13	16 (18.4)
Del17	1 (1.1)
Del13, Del17	6 (6.9)
Trisomy	9 (10.3)
t (11,14)	8 (9.2)
Other	5 (5.7)
Unknown	82 patients
Induction chemotherapy	
VAD	48 (28.4)
VCD	42 (24.9)
TD	20 (11.8)
VD	33(19.5)
VTD	20 (11.8)
Other	6 (3.6)
Pre-transplant response	
Stringent complete response	20 (11.9)
Complete response	64 (38.1)
Partial response	64 (38.1)
Very good partial response	19(11.3)
Post-transplant response	
Stringent complete response	35 (20.7)
Complete response	97 (57.4)
Partial response	11 (6.5)
Very good partial response	20 (11.8)
Progressive disease	6 (3.6)
Maintenance	
Yes	30 (17.8)
No	139 (82.2)
Relapse post transplantation	
Yes	97 (58.8)
No	68 (41.2)
Patient required second transplantation	
Yes	11 (7.2)
No	142 (92.8)
Time of transplantation	
1997-2009	80 (47.3)
2010-2015	89 (52.7)

Data are number (%)

VAD (vincristine, doxorubicin and dexamethasone) , VCD (Velcade [Bortezomib], cyclophosphamide, and dexamethasone) , TD (thalidomide and dexamethasone) , VD (Velcade [Bortezomib] and dexamethasone), VTD (Velcade [Bortezomib], thalidomide, and dexamethasone)

poor prognosis. These numbers match the older data before the introduction of proteasome inhibitors, since around 40% of our cohort was treated with the VAD or TD protocol; 28.4% of patients received VAD as the initial standard induction therapy. With the introduction of novel agents, the standard induction became VCD, which was given to 24.9% of patients.

The pre-transplant evaluation showed that 50% of patients achieved a CR or better (using IMWG 2014 response criteria). This number improved to 78.1% post-transplant. These rates are consistent with other published series of real-world experience.[7] The use of maintenance after ASCT was not common (17.8%) in our practice until recently when it was integrated as standard therapy in our protocols. The use of maintenance therapy in our protocol is optional because of the reported lack of survival benefit of maintenance

Table 2a. Progression- free survival analysis by univariate Cox regression.

	Coefficient (B)	Standard error	Wald χ^2	*P* value	Hazard ratio (95% CI)
Age	0.017	0.011	2.085	.149	1.017 (0.99-1.04)
Gender (female)	0.207	0.209	0.986	.321	1.23 (0.82-1.85)
ISS stage					
I					
II	-0.107	0.299	0.129	.719	0.90 (0.50-1.61)
III	-0.103	0.269	0.148	.701	0.90 (0.53-1.53)
Cytogentics by FISH					
Normal					
Del13	0.698	0.396	3.109	.078	2.01 (0.93-4.37)
Del17	0.639	1.03	0.385	.535	1.90 (0.52-14.28)
Del13, Del17	0.082	0.558	0.021	.884	1.09 (0.36-3.24)
Trisomy	0.294	0.471	0.391	.532	1.34 (0.53-3.38)
t (11,14)	-0.226	0.506	0.2	.655	0.80 (0.30-2.15)
Others	0.443	0.509	0.758	.384	1.56 (0.58-4.22)
Transplantation period	0.255	0.217	1.376	.241	1.29 (0.84-1.98)
Pre-ASCT evaluation					
Stringent complete response					
Complete response	1.01	0.446	5.137	.023	
Partial response	1.357	0.437	9.645	<.001	
Very good partial response	0.907	0.528	2.949	.086	

Table 2b. Progression-free survival analysis by multivariate Cox regression.

	Coefficient (B)	Standard error	Wald χ^2	*P* value	Hazard ratio (95% CI)
Age	0.019	0.011	2.741	.10	1.02 (0.99-1.04)
Gender (female)	0.224	0.212	1.118	.29	1.25 (0.83-1.90)
Pre ASCT evaluation					
Stringent complete response					
Complete response	1.00	0.45	4.98	.03	2.72 (1.13-6.53)
Partial response	1.35	0.44	9.53	<.001	3.87 (1.64-9.14)
Very good partial response	0.96	0.53	3.27	.07	2.61 (0.92-7.40)

Table 3a. Overall survival analysis by univariate Cox regression.

	Coefficient (B)	Standard error	Wald χ^2	*P* value	Hazard ratio (95% CI)
Age	0.01	0.02	0.28	.59	1.01 (0.98-1.05)
Gender (female)	-0.28	0.38	0.54	.462	0.76 (0.36-1.59)
ISS stage					
I					
II	-0.78	0.54	2.04	.15	0.46 (0.16-1.34)
III	-0.36	0.44	0.66	.42	0.70 (0.30-1.66)
Cytogenetics by FISH					
Normal					
Del13	1.83	0.58	10.01	<.001	6.22 (2.01-19-30)
Del17	0.87	1.11	0.62	.43	2.38 (0.27-20.80)
Del13, Del17	-0.09	1.08	0.01	.93	0.91 (0.11-7.59)
Trisomy	0.26	1.11	0.05	.82	1.30 (0.15-11.49)
t (11,14)	-0.37	1.08	0.11	.74	0.69 (0.8-5.79)
Transplantation period	0.70	0.40	3.06	.08	2.02 (0.92-4.44)
Pre-ASCT evaluation					
Stringent complete response					
Complete response	1.47	1.04	2.02	.16	4.36 (0.57-33.18)
Partial response	1.35	1.03	1.70	.19	3.84 (0.51-29.13)
Very good partial response	1.37	1.16	1.41	.24	3.94 (0.41-37.92)
Post-ASCT evaluation					
Stringent complete response					
Complete response	1.27	0.61	4.29	.04	3.56 (1.07-11.84)
Partial response	1.66	0.93	3.16	.08	5.25 (0.84-32.63)
Very good partial response	0.67	0.92	0.53	.47	1.96 (0.32-11.86)
Progressive disease	1.72	1.17	2.15	.14	5.59 (0.56-55.73)

Table 3b. Overall survival analysis by multivariate Cox regression.

	Coefficient (B)	Standard error	Wald χ^2	*P* value	Hazard ratio (95% CI)
Age	0.01	0.03	0.06	.81	1.01 (0.95-1.08)
Sex (female)	-0.24	0.67	0.13	.72	0.79 (0.21-2.95)
Cytogenetics by FISH					
Normal					
Del13	1.697	0.634	7.169	<.001	5.46 (1.58-18.89)
Del17	1.394	1.483	0.884	.347	4.03 (0.22-73.69)
Del13, Del17	-0.206	1.185	0.03	.862	0.81 (0.08-8.30)
Trisomy	-0.071	1.225	0.003	.954	0.93 (0.09-10.27)
t (11,14)	-0.41	1.107	0.137	.711	0.66 (0.08-5.81)
Post-ASCT evaluation					
Stringent complete response					
Complete response	1.323	1.108	1.426	.23	3.76 (0.43-32.94)
Partial response	2.123	1.297	2.679	.10	8.36 (0.66-106.13)
Very good partial response	0.378	1.437	0.069	.79	1.46 (0.09-24.41)
Progressive disease	2.54	1.818	1.951	.16	12.68 (0.36-447.61)

therapy and side effects.

The excellent survival rates in this study can probably be attributed to the availability of novel agents for salvage therapy, but is also probably related to the younger age of the patients treated in this cohort. These survival rates compare favorably with reported rates,[15,16] and merit further investigation to determine whether there are significant differences in the biology and pharmacogenomics in Saudi Arabia. Interestingly, there were statistically significant differences in OS in the era of stem cell transplantation (before or after 2010) with a better outcome for the older era of transplant before 2010 despite advances in novel therapies and the improvement of supportive care. This may be explained by the fact that patients transplanted before 2010 were younger compared to those after 2010 (mean age 48.7 vs 52.1 years, respectively, *P*=.017). Out of 169 patients, only one patient died during the first 100 days after ASCT (<1%). This death was related to ovarian carcinoma rather than MM or transplant complications, which indicates that ASCT is a safe treatment modality in MM.

In summary, this study suffers from the usual limitations of a retrospective analysis using registry-level data. In addition, the study period was long and we used 2006 response criteria, but the study still provides essential insight into the treatment outcomes of MM in Saudi Arabia. Additionally, this report may serve as a reference for future studies in the Saudi population. We report a higher OS than what is reported internationally and a very low ASCT-related mortality (<1%), which is probably related to the younger MM population. Further studies are needed to investigate the differences in biology, pharmacogenomics, and characteristics of the disease between patients in Saudi Arabia and other countries.

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