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Research Article

The Outcome of Autologous Stem Cell Transplantation in Adolescent and Young Adult Patients with Multiple Myeloma

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Abstract

Objectives: Multiple myeloma (MM) is a disease of the elderly and peaks at 60-to-70 years of age. The disease is rarely observed in young age groups. The incidence of MM is 2% among the patients under 40 years of age.

Methods: In this retrospective study, we analyzed the results of MM patients in the adolescents and young adults (AYA) age group who were treated in our center between January 2010 and July 2018.

Results: Of the 212 MM patients, 7% (15/212) were in the AYA age group. The median progression-free survival (PFS) was 20.3 months, and the median overall survival (OS) was 41.5 months among patients in the AYA age group. In the group of patients who were over 40 years of age, the median PFS was 19.07 months, and the median OS was 30.1 months. At the time of diagnosis, the patients in the group that was 40 years of age or older were, more frequently International Staging System (ISS) 2 and ISS 3, while patients in the AYA group were more often ISS 1.

Conclusion: As the goal is to achieve longer OS, and the incidence of comorbidities in younger patients is low, augmented treatments should be considered in AYA age group MM patients.

Keywords: Autologous hematopoietic stem cell transplantation, adolescent young adult, multiple myeloma

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Multiple myeloma (MM) is the second most common hematologic malignancy. Significant improvements in the prognosis of MM have recently been observed in the era of novel agents. Agents such as lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, and panobinostat have begun to be used in the treatment of relapsed/refractory MM. Patients treated with these new agents have better overall survival (OS) than patients who have never received these agents.[1,2] However, even with new agents, some patients develop resistance over time and continue to experience recurrent relapses; therefore, long-term disease control cannot be achieved. Allogeneic stem cell transplantation is a potential curative option for high-risk cytogenetic fit patients who have early relapses after autologous stem cell transplantation (ASCT).[3,4] The prognosis of MM patients is quite heterogeneous. Therefore, it is very important to discover every prognostic factor to predict survival and new treatment strategies should be considered for patients who are expected to have shorter OS. Factors about the host and the disease itself such as the properties of the tumor, the tumor microenvironment, age, and comorbidities have

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been shown to be significant prognostic factors.[5,6] MM is a disease of the elderly, with peaks in incidence at ages 60–70.[7,8] The disease is rarely observed in younger age groups. The incidence of MM is 2% among patients under 40 years of age. Patients who are 15–39 years old are referred to as adolescents and young adults (AYA).[8–11] Because MM is a disease affecting older individuals, the studies about MM incidence, clinical features, and survival rates are limited in the AYA age group.[5, 9–12] In this study, we aimed to analyze the outcomes of AYA MM patients who underwent ASCT at our bone marrow transplantation center.

Methods

The transplantation results of MM patients who underwent ASCT at the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Bone Marrow Transplantation Center between January 2010 and July 2018 were analyzed retrospectively. The patients were divided into 2 groups: an AYA age group and a ≥40 years of age group. Age, gender, MM subgroup, Durie Salmon (DS) and International Staging System (ISS) stages, the number of chemotherapy lines they received prior to transplant, their history of radiotherapy (RT), the dose of the conditioning regimen they received (melphalan 140 mg/m^2, 200 mg/m^2), the quantity of infused CD34+ stem cells, and the pre-transplant responses of the patients are given in Table 1. ISS, Revised ISS (R-ISS), and DS stages were used for risk classification. We evaluated the response to the treatment 3 months after ASCT. The evaluation of the treatment response was carried out according to the criteria of the International Myeloma Working Group (IMWG).[13]

Patients were mobilized utilizing 10 µg/kg subcutaneous granulocyte colony stimulating factor (G-CSF). If the

Table 1. Characterics of the patients in AYA age group and ≥40 years group

Age (median)	36 (25-39)	56 (40-81)
Gender	Female (n): 3/Male (n): 12	Female (n): 82/Male (n): 115
MM Group		
	Heavy Chain (n): 10	Heavy Chain (n): 148
	Light Chain (n): 4	Light Chain (n): 42
	Non-Secretory (n): 1	Non-Secretory (n): 4
		Unknown (n): 3
ISS	ISS I (n): 12	ISS I (n): 53
	ISS II (n): 2	ISS II (n): 60
	ISS III (n): 1	ISS III (n): 52
		Not evaluated : 32
Durie Salmon Stage	DS1 (n): 1	DS1 (n): 9
	DS2 (n): 1	DS2 (n): 16
	DS3 (n): 13	DS3 (n): 164
		Not evaluated (n): 8
Pre-transplantation response	CR: 57.14%	CR: 37.5%
	VGPR: 21.42%	VGPR: 24.47%
	PR: 14.18%	PR: 27.6%
	Stable: 7.26%	Stable: 7.81%
	Progressive: none	Progressive: 2.6%
Melphalan Dose	200mg/m^2 (n): 15	140mg/m^2 (n): 22
		200mg/m^2 (n): 175
Chemotherapy Line(s)	1 line (n): 4	1 line (n): 53
	2 lines(n): 9	2 lines (n): 111
	3 lines (n): 1	3 lines (n): 24
	Not evaluated (n): 1	4 lines (n): 3
		5 lines (n): 1
		Not evaluated (n): 5
Radiotherapy history	Applied: 2	Applied: 33
	Not-applied: 13	Not-applied: 164
Infused CD34+ cell (median)	4.620x106/kg	4.625x106/kg

MM: Multiple Myeloma; ISS: International Staging System.

mobilization was poor, they were mobilized by high dose cyclophosphamide (4.000 mg/m^2) and G-CSF. If required, patients were mobilized with plerixafor after G-CSF was subcutaneously applied for 4 days at a dose of 2*5 µg/kg, and plerixafor at a dose of 0.25 mg/kg/day was applied on the 4th day at 5:00 p.m. The stem cells from peripheral blood were collected with a continuous flow of blood cell separator (Fresenius Kabi, COM.TEC, Germany). Each process of apheresis lasted for approximately 2–4 hours, and 2–2.5 times the blood volume was processed.

Tandem transplant patients described as having a second transplant within 6 months without progression or relapse after the first ASCT, were not included in the study. Post-transplant OS was described as the duration between the date of transplantation to death or the duration between the date of transplantation until the last follow-up for the surviving patients. Post-transplant progression-free survival (PFS) was described as the duration from the date of transplantation to progression or to the date of death or the duration that passed until the last follow-up for the patients with no disease progression. Neutrophil engraftment was defined as the first day when the absolute neutrophil count (ANC) was >500/mm^3 or 1.000/mm^3 without any support for 3 consecutive days, and platelet engraftment was defined as the first day when platelet count was >20.000/mm^3 or 50.000/mm^3 without transfusion support for 3 consecutive days. Transplant-related mortality (TRM) was defined as death within 100 days after transplantation.[14]

IBM SPSS Statistics (version 21) software was used for statistical analysis. Descriptive statistics were used to summarize the data. Categorical data were expressed as a ratio, and numerical data were expressed as a median and a mean±standard deviation. Chi-square and Fisher exact tests were used to evaluate the differences in ISS and DS stage distribution and in pre and post-transplant response distribution between age groups. The differences between neutrophil and platelet engraftment times across age groups were examined by the non-parametric Mann–Whitney U test. Kaplan-Meier survival analysis for PFS and OS and log-rank tests were used to examine the factors affecting survival. P values of ≤0.05 were considered statistically significant.

Results

212 MM patients underwent ASCT between January 2010 and July 2018 at our center, and 7% (15/212) of them were between 15 and 39 years of age (the AYA group). In the AYA group, there was a male predominance; 12 of the 15 patients were males (80%). The median age in the AYA age group was 36 (range: 25–39). The median age was 36 years for males and 30 years for females. MM subgroup distribution of the AYA age group was as follows: 10 heavy chains, 4 light chains, and 1 non-secretory myeloma. When the AYA age group patients were compared with the ≥40 years age group patients, we did not observe any statistically significant differences in terms of the MM subgroups (p=0.380).

At the time of diagnosis, 1 patient was Durie Salmon (DS) stage 1, 1 patient was DS 2, and 13 patients were DS 3 in the AYA age group. We did not observe any statistically significant differences between the AYA age group and the ≥40 years age group in terms of DS stage (p=0.855). 12 patients were ISS 1, 2 patients were ISS 2, and 1 patient was ISS 3 in the AYA age group at the time of diagnosis. The majority of the patients were ISS 1 at the time of diagnosis in the AYA age group. When we compared the AYA age group patients and the patients ≥40 years we observed a statistically significant difference regarding the ISS stage (p=0.022**).

After the induction treatment, complete response (CR), very good partial response (VGPR), partial response (PR) and stable disease rates in the AYA age group were 57.14%, 21.42%, 14.18%, and 7.26% respectively. In the AYA age group, progressive disease was not observed after induction treatment. In the patients ≥40 years age group; CR, VGPR, PR, stable disease and progressive disease rates were 37.50%, 24.47%, 27.6%, 7.81%, and 2.62% respectively at the end of induction treatment. We did not find a statistically significant difference between the two age groups regarding the response rates at the end of induction treatment (p=0.238).

Post-transplant response was evaluated 3 months after ASCT and CR, VGPR, PR, progressive disease rates were found 46.7%, 6.7%, 3.2% and 13.3% respectively in the AYA age group. No stable disease was observed. 26.7% of the patients' post-transplantation responses could not be reached in the records. In ≥40 years age group; post transplant CR, VGPR, PR, stable disease, progressive disease rates were 67%, 6.6%, 15.2%, 1% and 1% respectively. In this age group, 9.1% of the patients' post-transplantation responses could not be reached in the records. We found a statistically significant difference regarding the post-transplantation responses when the AYA age group and ≥40 years age group were compared. In the AYA age group there was a higher progresive disease rate after ASCT (p=0.004).

In both age groups neutrophil engraftment was observed on median 11 days and platelet engraftment was observed on median 12 days after ASCT.

TRM was 6.7% in the AYA age group and 1% in ≥40 years age group. Although TRM rate was higher in the AYA age group, we did not find a statistically significant difference between the AYA age group and ≥40 years age group regarding TRM rates (p=0.198).

Median post transplant PFS was 20.3 months and me-

dian post transplant OS was 41.5 months in the AYA age group. Median post transplant PFS was 19.07 months and median post transplant OS was 30.1 months in ≥40 years age group. Although median post transplant PFS and post transplant OS were higher in the AYA age group patients, we did not find a statistically significant difference regarding post transplant PFS and OS between 2 groups (p=0.921, p=0.135, respectively).

We did not find any statistically significant impact of MM subgroup, the number of chemotherapy lines received before transplantation, radiotherapy (RT) history, infused CD34+ stem cell quantity, pre and post transplantation responses on post transplant OS and PFS (Table 2).

Discussion

MM is a disease of elderly beause of this, the literature about the outcome of ASCT in AYA age group MM patients is limited. Studies in Western countries showed that the incidence of MM is only 2% under the age of 40 years and only 0.3% under the age of 30 years.[8–11] To make risk adapted strategies for the treatment of MM, we have to know more about the outcome of specific age group patients. As AYA age group MM is very rare, we aimed to analyze ASCT outcome of AYA age group MM patients.

In the study conducted by Blade and Kyle including 4081 patients in United States of America, MM incidence in AYA age group was found 3%.[15] Yanamandra et al.[16] found the incidence of AYA MM as 10%. In our study, 7% of the MM patients were under the age of 40 and 1.4% were under the age of 30. These rates are higher than the western countries but lower than the rates reported in India. This result suggests that the age of MM decreases gradually from west to east.

In previous studies, it has been found that there is a negative correlation between age and OS therefore it has been considered as a prognostic factor. Moreover, age has a critical impact on bone marrow transplantation.[17,18] In the study of Sagaster et al., OS was 23.4 months in <45 years old ISS 3 MM patients, the median OS could not be reached in ISS 1 and 2 stages throughout the follow-up duration of the study. In the same study, in ISS 3 MM patients, OS was found 24.6 months in the 45-70 age group and 32 months in >70 years of age.[11] In the study by Yanamandra et al., 3-year OS was found 73.7% in the ISS 3 AYA age group patients.[16] In our study, 80% of the AYA age group patients were ISS 1. Only 1 patient was ISS 3. In our study, median post transplant PFS was 20.3 months and OS was 41.5 months in the AYA age group. Median post transplant PFS and OS in patients ≥40 years of age were 19.07 months and 30.1 months, respectively. Although the median PFS and OS were longer in the AYA age group patients, we did not find any statistically significant difference regarding PFS and OS when compared with patients ≥40 years of age (p=0.921, p=0.135).

In the study by Sagaster et al.,[11] they classified 250 MM patients in 3 age groups; <45 years, 45-70 years and >70 years of age, no statistically significant difference was found between the age groups and MM subgroups. Similarly, in our study, no statistically significant difference was found between the AYA age group MM patients and other MM patients regarding MM subgroups.

In the study conducted by Yanamandra et al. while the majority of MM patients in AYA age group were ISS 3, in our study the majority of the patients in the AYA age group were ISS 1 at the time of diagnosis.[16] When the AYA age group patients were compared with the patients over 40 years of age regarding the ISS stage distribution, a statistically significant difference was observed (p=0.022*). However, the comparison of the AYA age group patients and patients ≥40 years of age did not yield a statistically significant difference regarding DS stage distribution (p=0.855).

Table 2. Impact of selected variables on OS and PFS

	OS (p)	PFS (p)
Myeloma subgroup	0.364	0.317
Chemoterapy lines received	0.951	0.157
Radiotherapy history	0.277	0.292
Number of infused CD34+ cell	0.141	0.317
Pre-transplantation response	0.065	0.273
Post-transplantation response	0.060	0.273

OS: overall survival; PFS: progression free survival.

Conclusion

In conclusion, although MM is an older age disease, it may also be seen in AYA age group patients. The standard approach to AYA patients is performing upfront ASCT after induction treatment. We found that post transplant OS and PFS in the AYA age group are similar to patients who are ≥40 years of age, this shows that in this younger age group, new treatment strategies targeting longer OS along with minimal toxicity should be developed. As the goal is the longer OS and the incidence of comorbidities in younger patients is low, augmented treatments should be considered. AYA age group MM is very rare but these are the patients who we have to reach the longest PFS and OS therefore substantial studies are required to find out the best treatment approach for AYA age group patients.

Disclosures

Ethics Committee Approval: Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Health Practice and Research Center Clinical Research Ethics Committee (02.10.2019-2019-10/400).

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