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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Salvage Autologous Hematopoietic Stem Cell Transplantation Versus Chemoimmunotherapy in Relapsed Multiple Myeloma Patients After First Transplantation; Single Center Data

Otolog Kök Hücre Nakli Sonrasında Nüks Etmiş Multiple Miyeloma Hastalarında Salvage Otolog Kök Hücre Nakil Tedavisinin Kemoimmünoterapi ile Karşılaştırılması; Tek Merkez Verisi

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Abstract

Objectives: Multiple myeloma (MM) is an uncurable disease and standard therapy for relapsed MM is still not clear. We aimed to compare salvage treatments for relapsed refractory MM.

Materials and Methods: Sixty patients who relapsed after first autologous stem cell transplantation (ASCT) were analyzed. Twenty-seven patients were treated with salvage chemoimmunotherapy (CIT). Thirty-three were treated with salvage ASCT.

Results: There was no difference between treatment arms in terms of gender, age and disease characteristics. Median progression-free survival (PFS) was significantly better in ASCT group than CIT group (25 months vs. 12 months; p=0.01). PFS rates on the first and second year were also better in ASCT group. Median overall survival in ASCT group was longer than CIT (73 vs. 30 months), although it did not reach a statistical significance (p=0.09). Time to achieving the best response after ASCT and CIT was 1 (0-9) month versus 6.5 (2-15) months (p=0.02). All grade toxicities were similar in both groups (ASCT 57.6% vs. CIT 48.1%) (p=0.6). Grade 3 or 4 toxicities were similar (ASCT 19%, CIT 13%) in both groups (p=0.4). In the approximate cost analysis made with current pricing in December 2022 in our country, ASCT was more economical than CIT (380 600 € vs. 393 860 €).

Conclusion: Salvage ASCT may provide longer PFS with similar toxicity profile and more cost-effective therapy profile than salvage CIT. It is suggested that earlier and better responses, long-term PFS can be achieved with salvage ASCT.

Key Words: Multiple Myeloma, Relapsed, Salvage Transplantation, Chemoimmunotherapy, Second Autologous, Stem Cell Transplantation

Öz

Amaç: Tedavi alanındaki yeni gelişmelere rağmen kombinasyon kemoimmunoterapileri ve ardından otolog hematopoetik kök hücre nakli (OKHN) multiple miyelom (MM) tedavisinin temelini oluşturmaktadır. OKHN ile uzun ve derin yanıtlar elde edilse de MM hala kür sağlanamayan ve nüksün çoğu zaman kaçınılmaz olduğu bir hastalıktır. Çalışmada MM hastalarında OKHN sonrası verilen kurtarma tedavilerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmada, OKHN sonrası nüks gözlenen 60 hasta geriye yönelik olarak analiz edildi. Hastalar nükste aldıkları tedaviye göre ikiye ayrıldı. Birinci gruta kurtarma tedavisi amacıyla kemoimmünoterapi (KİT) verilmiş olan 27 hasta; ikinci grupta ise kurtarma tedavisi olarak ikinci OKHN yapılmış 33 hasta incelendi.

Bulgular: KİT ve ikinci OKHN hasta grupları arasında cinsiyet ve yaş dağılımları açısından fark yoktu [kadın/erkek: 11 vs 13/16 vs 20; yaş 55 (33-71) vs 59 (44-70)]. Ortanca ilerlemesiz sağkalım ikinci OKHN grubunda KİT grubuna göre anlamlı olarak daha iyi tespit edildi (ilerlemesiz sağkalım; OKHN grubunda 25 ay vs KİT kolunda 12 ay; p=0,01). Toplam sağkalım, istatistiksel olarak anlamlılığa ulaşmamış

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Öz

olsa da ikinci OKHN grubunda daha yüksek bulundu (73'e karşı 30 ay; p=0,09). Tedaviler sonrası en iyi yanıta ulaşma süresi OKHN kolunda ortanca 1 ay (0-9) iken KİT kolunda 6,5 ay (2-15) idi (p=0,02). Tüm derece toksisiteler iki grupta benzer bulundu (OKHN %57,6 vs KİT %48,1) (p=0,6). Yine derece 3 veya 4 toksisite açısından iki grup arasında fark bulunmadı (OKHN %19, KİT %13) (p=0,4). Ekonomik analizde ise OKHN, KİT'ye kıyasla daha ucuz bulundu.

Sonuç: Birinci OKHN sonrası nüks tedavisinde ikinci OKHN, kurtarma amaçlı verilen KİT'ye göre daha uzun ilerlemesiz sağkalım sağlamakla birlikte benzer toksisite profiline sahiptir. Kurtarma tedavisi amacıyla yapılan ikinci OKHN ile KİT'ye kıyasla daha hızlı, daha iyi yanıtlar ve daha uzun bir ilerlemesiz sağkalım daha ekonomik şekilde sağlanabilir.

Anahtar Kelimeler: Multiple Miyelom, Nüks, Salvage Nakil, Kemoimmunoterapi, İkinci Otolog, Kök Hücre Nakli

Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder and the second most common hematological malignancy. According to United States data, the projected number of new myeloma cases for 2022 is 34,470 and the expected number of deaths due to myeloma is 12,640 (1). Although new myeloma specific agents have been developed in recent years, for newly diagnosed MM patients, induction therapy followed by high-dose therapy followed by autologous stem cell transplantation (ASCT) is still the standard for the treatment of incurable disease, which can only be treated with easy and tolerable medications (2-6). The role of second transplantation in relapsed disease after first ASCT is not clear yet.

The rate of patients that can be treated with novel drugs such as thalidomide, bortezomib, lenalidomide, carfilzomib, pomalidomide has increased from 60% to 80% in the last 10 years. Parallel to this, very good partial and better response rates increased after the first-line treatment (36.1% vs. 53.5%). After front-line treatment, ASCT can be performed in 77% of patients under 65 years of age. The reported recurrence rates in the first year and after the first year after ASCT are 14% and 86% respectively (7,8).

The standard for salvage therapy after ASCT remains unclear. Treatment options for relapsed myeloma include combined antimyeloma treatment based on proteosome inhibitors, immunomodulatory drugs, monoclonal antibodies, salvage autologous transplantation and allogeneic stem cell transplantation. There is no study showing the superiority of new drug combinations versus second ASCT, nor is there a prospective, randomized study comparing these treatment modalities (9-11).

In our single-center, retrospective study we evaluated the efficacy and cost effectiveness of second ASCT versus conventional chemo immunotherapy as salvage therapy, its effects on progression-free survival (PFS) and overall survival (OS), and outcomes in previously transplanted relapse patients.

Materials and Methods

Patients diagnosed with MM in the Hematology Department of Gazi University Faculty of Medicine were evaluated retrospectively. Between the dates of data collection period, 223 MM patients underwent ASCT in our center. Patients who underwent ASCT and relapsed after the first ASCT were included in the study. Among these patients, the data of 60 patients were analyzed. Patients had indications for treatment because of biochemical relapse and/or symptoms of MM (CRAB findings) such as hypercalcemia, renal failure, and anemia and bone lesions. Patients were divided into two groups according to the treatment type. First group [salvage chemoimmunotherapy (CIT)] (n=27) was treated with CIT because of patient reluctance to transplantation. Second group (n=33) (salvage ASCT) was treated with second ASCT as salvage therapy. Patients with relapse within the first 6 months after the first transplantation were not included in the analysis in order to avoid bias in the choice of salvage treatment in these two groups.

Ethics Committee approval was received from Gazi University with the number 77082166-302.08.01.

Statistical Analysis

Statistical tests were performed using SPSS 16.0 version. Mean and median values of the two groups were compared using Student's t-test or Mann-Whitney U test. PFS and OS were calculated by Kaplan-Meier method. The log-rank method was used to compare survival. P-value less than 0.05 was considered significant.

Results

A total of 60 patients were analyzed. Salvage ASCT was performed in 33 patients and 27 patients were treated with salvage CIT.

The median age between salvage CIT group and salvage ASCT group was similar [55 (min: 33 max: 71) years vs 59 (min: 44- max: 70) years respectively (p=0.46)]. Gender distributions were not different (numbers of male/female patients were

16/11 in CIT group, 20/13 in ASCT group, p=0.91). PFS after first transplantation for CIT group was 7-60 months, with a median of 19 months while it was 8-92 months with a median 25 months in ASCT group. Follow-up period of patients in CIT group was median 68 months (min: 11- max: 139) and 97 months (min: 35- max: 202) in salvage ASCT group. Disease prognostic scores, responses before and after first ASCT were summarized in Table 1. All patients underwent first ASCT after melphalan 200 mg/m^2 conditioning regimens. Best response after first ASCT, time to achieving best response, time with the best response and PFS after first ASCT were statistically similar in both groups with p-values of 0.42; p=0.50; p=0.55 and p=0.25 respectively. Bone marrow plasma cell ratios before the salvage ASCT or CIT were also similar in both groups (p=0.35). Salvage chemotherapies mostly consisted of triple agents. First-line salvage therapies after first ASCT were cyclophosphamide, bortezomib and dexamethasone (CyBord) for 8 patients, bortezomib, lenalidomide and dexamethasone (VRD) for 8 patients, bortezomib, thalidomide and dexamethasone (VTD) for 3 patients and other bortezomib or lenalidomide-based chemotherapies for 8 patients. Second-line salvage CIT was VRD in 4 patients, lenalidomide and dexamethasone in 4 patients and combinations containing bortezomib, carfilzomib, lenalidomide and thalidomide in other 11 patients. Third-line salvage therapy also consisted of lenalidomide, carfilzomib, pomalidomide, thalidomide-based therapies and allogeneic stem cell transplantation for 2 patients. Before salvage ASCT, induction treatment was given to 16 patients while 17 patients were directly transplanted. Among the 16 patients who received induction therapy, 13 received only one stage treatment, while 3 received two stages of treatment before second ASCT. Melphalan was used 140 mg/m^2 dosage for second transplantation.

Outcomes of salvage CIT and salvage ASCT were shown Table 2. The CR as best response after salvage ASCT was achieved in higher proportion of patients compared with salvage CIT group (62.5% vs. 44%, p=0.04). Time to achieving best response after salvage ASCT and salvage CIT was 1 (0-9) month vs. 6.5 (2-15) months (p=0.02). Compared to the salvage CIT group, the PFS rates were significantly higher in salvage ASCT group (71% and 46.9% vs. 59.3% and 17%; in the first and second year respectively p=0.01). Although not reaching statistical significance, median OS duration for salvage ASCT group were longer than salvage CIT (73 vs. 30 months; p=0.09). OS rates were also higher in ASCT group than CIT group at 1st, 2nd, 5th year. Comparison of PFS and OS curves of salvage approaches is shown in Figure 1. At the end of the follow-up period, the patient survival rate was 30% in the CIT group and 66% in the ASCT group.

All grade toxicities were similar in both groups (salvage ASCT 57.6% vs. salvage CIT 48.1%) (p=0.6). Grade 3 or 4 toxicities were similar (salvage ASCT 19%, salvage CIT 13%) in both groups (p=0.4). Toxicity information was shown in Table 2.

According to the approximate cost analysis made with current reimbursement and drug price information valid in our country in 2022, the cost in the salvage ASCT arm has been found to be €380 600, while the cost in the salvage CIT arm was €393 860.

Table 1: The prognostic risk scoring of the patients, responses before and after the first ASCT

	CIT group (n=27)	ASCT group (n=33)	p-value
R-ISS			0.55
I	1	4	
II	5	10	
III	6	7	
Durie-Salmon stage			0.27
I	0	3	
II	3	4	
III	22	23	
Response before 1st ASCT			0.63
≥PR	26 (96.2%)	30 (90.9%)	
<PR	1 (3.8%)	3 (9.1%)	
Response after 1st ASCT			0.42
≥PR	25 (92.6%)	32 (97%)	
<PR	2 (7.4%)	1 (3%)	

CIT: Chemoimmunotherapy, ASCT: Autologous stem cell transplantation, R-ISS: Revized international staging system, PR: Partial remission

Discussion

Table 2: Outcome of salvage therapy

	CIT group	ASCT group	p
Best response			
CR	44.0%	62.5%	
VGPR+PR	14.8%	16.5%	0.04
<PR	41.2%	21%	
Time to achieving best response (months)	6.5 (2-15)	1 (0-9)	0.02
PFS (median, month)	12	25	
PFS rate at 1st year	59.3%	71.0%	0.01
At 2nd year	17.0%	46.9%	
At 5th year	11.4%	27.3%	
OS (median, month)	30	73	
OS rate at 1st year	77.8%	84.7%	0.09
At 2nd year	23.7%	74.2%	
At 5th year	23.7%	42.3%	
All grade toxicities	48.1%	57.6%	0.6
Grade 3-4 toxicities	13%	19%	0.4

CIT: Chemoimmunotherapy, ASCT: Autologous stem cell transplantation, CR: Complete remission, VGPR: Very good partial remission, PR: Partial remission, PFS: Progression free survival, OS: Overall survival

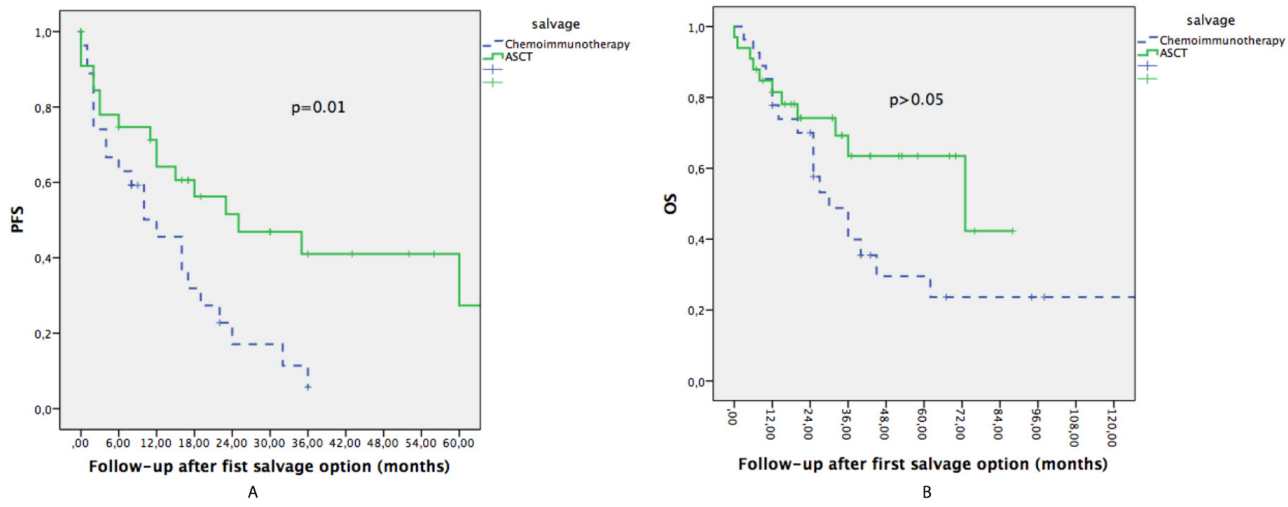

Figure 1: A) Progression free survival, **B)** Overall survival curves after salvage therapy

ASCT: Autologous stem cell transplantation, PFS: Progression-free survival, OS: Overall survival

ASCT is the preferred treatment for newly diagnosed myeloma patients who has a better response than partial remission after combined initial therapy who are eligible for transplantation. According to the Consensus Conference of the American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplantation Clinical Trials Network and International Myeloma Working Group; second ASCT is recommended for relapsed myeloma patients who remain in remission for more than 18 months after primary treatment including ASCT (12). Nevertheless, prospective randomized studies comparing new therapeutic agents with salvage second ASCT therapy are still needed for patients who relapse less than 18 months after primary therapy (13-15).

According to the results of many retrospective studies in the literature, the positive contribution of second ASCT to PFS and OS in patients with chemo sensitive disease showing long-term remission after the first ASCT is clear. The most important factors affecting this contribution are the number of previous treatments the patient has received, the depth and duration of the treatment response. Additionally, this treatment method has an acceptable toxicity profile (16-20).

In a multicenter retrospective evaluation of second ASCT patients, excluding tandem ASCT, PFS at 1 year, 3 years and 5 years was reported 47%, 13% and 5%, while OS rates were 83% 46% and 29%, respectively (17).

In a retrospective study of 588 patients, the second ASCT was compared with conventional cytotoxic therapy and proteosome inhibitor or immunomodulatory therapy-based regimens. The median OS was significantly prolonged with the second ASCT compared to cytotoxic treatment and novel drug groups (4 years vs. 2.5 years vs 3.3 years) (16).

A real-world experience data from Japanese also showed that a salvage second ASCT had a favorable OS than standard salvage regimens (21).

There are limited numbers of prospective studies on salvage ASCT. In one of these studies, PFS and OS were significantly longer in patients who received a salvage ASCT than weekly cyclophosphamide group (PFS 19 vs. 11 months, p<0.0001 and OS 67 months vs. 52 months, p=0.0169) (22).

In a prospective, phase-3 study, continuous lenalidomide dexamethasone treatment without transplantation was compared with salvage ASCT after reinduction with lenalidomide dexamethasone treatment in patients with relapsed myeloma. PFS was longer in the salvage ASCT patients and median OS was not reached in these patients, while median OS was 62.7 months in CIT patients (9). In another retrospective study single and double ASCT has been compared. PFS and OS were not different in both groups. However, it is noteworthy that the number of double ASCT patients in the study was significantly lower than single ASCT patients (17 vs. 211) (23).

We analyzed relapsed MM patients with no difference in gender, age, number of previous treatments, treatment responses, PFS and plasma cell infiltration rates. We continued to the analysis, after showing statistically similar aged, similar responses to the first anti-myeloma treatment and similar PFS after first ASCT in order to avoid patient selection bias. Most of our study's results were parallel to the retrospective and prospective studies published before. All subgroup response rates were found to be better in patients with salvage ASCT than in the CIT group. The time to achieving the best response after salvage therapy was significantly faster in the salvage ASCT patients. PFS rates were significantly better in the salvage ASCT group at the first year, and this significance also continued

at second year of the follow-up period. Although the OS was longer in the salvage ASCT group, it did not reach a statistical significance. Nevertheless, survival status of the patients was found to be significantly better in salvage ASCT group at the end of the follow-up period. Second ASCT as salvage, which was found to be an effective treatment, did not differ in terms of toxicity, side effects and treatment-related morbidity compared with the CIT group. In our study, the cost analysis of the treatments received was made and ASCT treatment was found to be more cost effective than CIT. We think that our study makes an important contribution to the literature with this analysis. Although increasingly targeted therapies are being developed in all areas of medicine, their cost should be thought as an important parameter, especially in developing countries.

Study Limitations

As for the limitations of the study, the most important limitation is that the study was not conducted in a prospective setting. Although there are many different treatment options in case of relapsed disease in MM, the analysis of patients with different treatments may seem to create a bias. However, due to the small number of patients and the reimbursement conditions in the relevant period in our country and the treatment options recommended in the guidelines according to the patient's condition, it was thought that it should not cause any problems in the analyses. Another limitation is in the number of patients, and by extending the follow-up period and increasing the use of new treatment agents, expanding the population of the study will further strengthen the results. Finally, after increasing the number of patients according to the characteristics of the patients, it is hoped that subgroup analyzes will determine which patients will benefit more from salvage transplantation.

Conclusion

In conclusion, for MM patients, second ASCT transplantation as salvage therapy should be considered as an alternative treatment modality to CIT, even more successful, economically more affordable, and a safe treatment in terms of toxicity and side effects in relapsed myeloma patients.

Ethics

Ethics Committee Approval: Ethics Committee approval was received from Gazi University with the number 77082166-302.08.01.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.C., Z.N.Ö., R.Ö., Z.A.Y., L.A.K., M.Y., Design: F.C., Z.N.Ö., R.Ö., Z.A.Y., L.A.K., M.Y., Data Collection or Processing: F.C., Z.N.Ö., R.Ö., Z.A.Y., L.A.K., M.Y., Analysis or Interpretation: F.C., Z.N.Ö., R.Ö., Z.A.Y., L.A.K., M.Y., Literature Search: F.C., Z.N.Ö., R.Ö., Z.A.Y., L.A.K., M.Y., Writing: F.C., Z.N.Ö., R.Ö., Z.A.Y., L.A.K., M.Y.

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