Research Paper / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2016;55(1):1-5

Autologous stem cell transplantation as a consolidation therapy in acute myeloid leukemia patients

Akut myelositer lösemi hastalarında konsolidasyon tedavisi olarak otolog hematopoetik kök hücre nakli uygulaması

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Abstract

Aim: Autologous stem cell transplantation (ASCT) is a treatment option as a consolidation therapy in acute myeloid leukemia (AML) patients. ASCT may improve disease free survival without effecting overall survival rates when compared with high dose Ara-C (HDARAC). ASCT becomes even more important after mortality and morbidity rates decrease with the new improvements. In this study, we analyzed the results of patients treated with ASCT after HDARAC therapy in the first remission.

Materials and Methods: AML patients diagnosed between 1998 and 2012 were retrospectively analyzed. After remission achieved by induction therapy and HDARAC consolidation therapy (3 gr/m^2, on alternate 3 days) 23 patients who were treated with ASCT were enrolled in the study. Statistical analysis and survival rates were analyzed by Graphpad 4.03 and the results were reported as median (range, minimum-maximum).

Results: The median time to neutrophil and thrombocyte engraftments was 12 (range, 8–28) days and 14 (8–100) days, respectively. We did not document any transplantation related mortality. Fifteen patients relapsed after ASCT and 13 of them died due to refractory disease. The median follow up period was 40 (range, 6-144) months. The median overall survival and disease free survival were 48 and 34 months, respectively. The overall survival rate was 32.2% at 144th month and the disease free survival rate was 27.3 % at 130th month.

Conclusion: ASCT may provide a long term disease free survival in AML patients after one cycle of induction chemotherapy and HDARAC as a consolidation therapy. Especially in AML patients without suitable related or unrelated donors, ASCT may provide a treatment option.

Keywords: Acute myeloid leukemia, autologous peripheral stem cell transplantation, consolidation, survival.

Öz

Amaç: *Akut myelositer lösemi (AML) olgularında remisyon sonrası konsolidasyon tedavisi olarak otolog hematopoetik kök hücre nakli (OHKHN) seçenekler arasında güncelliğini korumaktadır. Yapılan çalışmalarda, yüksek doz ara-C (YDAC) tedavisi ile karşılaştırıldığında, OHKHN'nin total sağkalımı etkilemediği halde hastalıksız sağkalımı arttırabileceği gösterilmiştir. Özellikle yeni gelişmelerle nakil sonrası mortalite ve morbiditenin azalması ile OHKHN'nin önemi artmıştır. Çalışmamızda, remisyon sağlanmasını takiben YDAC uygulaması sonrası OHKHN gerçekleştirilen hastaların sonuçları değerlendirilmiştir.*

Gereç ve Yöntem: *1998-2012 yılları arasında tanı alan tüm AML hastaları retrosprktif olarak incelendi. İndüksiyon kemoterapisi ile remisyon elde edildikten sonra YDAC (3 gr/m^2/gün, gün aşırı, 3 gün) konsolidasyonu uygulamasını takiben OHKHN uygulanan 23 AML hastası çalışmaya dahil edildi. İstatistik değerlendirmeler ve sağkalım hesaplamaları Graphpad 4.03 yazılımı ile yapılmış, sonuçlar ortanca (alt-üst sınır) olarak sunuldu.*

Bulgular: *Hastaların nötrofil ve trombosit yamanma süreleri median değerleri sırasıyla 12 (8-28) gün ve 14 (8-100) gün olarak bulundu. Nakil ilişkili ölüm izlenmezken nakil sonrası nüks eden 15 hastanın 13'ü refrakter hastalık nedeniyle kaybedildi. Ortanca 40 (6-144) aylık izlemde; ortanca total ve hastalıksız yaşam süreleri sırasıyla 48 ve 34 ay olup, 144. ayda total sağkalım oranı % 32.2 ve 130. ayda hastalıksız sağkalım oranı % 27.3 olarak bulundu.*

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Received: 07.01.2015 Accepted: 30.01.2015

Sonuç: *Birinci kür indüksiyon kemoterapisi ile tam remisyon sağlanan hastalarda YDAC uygulamasını takiben OHKHN uygulaması uzun süreli hastalıksız yaşam sağlayabilir. Özellikle uyumlu verici bulunamayan hastalarda YDAC pekiştirme tedavisinin ardından otolog nakil uygun bir seçenek olarak akılda tutulmalıdır.*

Anahtar Sözcükler: *Akut myelositer lösemi, otolog periferik kök hücre nakli, konsolidasyon, sağkalım.*

Introduction

Acute myeloid leukemia characterized by rapid and uncontrolled growth of myeloblasts, is the most common acute leukemia in adult patients. Although complete remission can be achieved with antracycline and cytarabine based induction chemotherapies, relapse is one of the most important obstacle to long term survival. Therefore consolidation therapies become very important in patients in complete remission to prevent relapse and improve survival (1, 2). Alternative strategies for post remission chemotherapies are high or intermediate dose cytarabine based chemotherapies, allogeneic stem cell transplantation, and autologous stem cell transplantation (ASCT) (3) but the best regimen is not clearly established. Although ASCT offers a much lower transplantation related death, relapse rate was higher possibly because of lack of graft versus leukemia effect and contamination of the harvest with leukemic cells when compared with allogeneic transplantation (4-6). The most important factors effecting the treatment option are the patients' characteristics like age and comorbidities, cytogenetic and molecular properties of the leukemic cells and the presence of a suitable donor (1). The mortality and morbidity rates of the each option should be considered on an individual basis.

National comprehensive cancer network suggests allotransplant for poor risk patients and consolidation chemotherapy for good risk patients. And a meta-analysis indicates that allogeneic stem cell transplantation increases the survival rates when compared with alternative strategies in patients with poor and intermediate risk factors (7). The most important handicap for allogeneic stem cell transplantation is absence of a suitable donor and the best treatment modality for these patients without a suitable donor is not well documented. Consolidation chemotherapies or autologous stem cell transplantation are the alternative treatment options. ASCT that improves the leukemia free survival rates is an effective option for adults with AML in first remission when compared with intensive consolidation chemotherapies (8-10). In a recent retrospective study in China, ASCT may be an alternative treatment option as effective as allogeneic transplantation especially in patients without suitable donors (11). Especially advances in supportive care reduced the transplant related mortality in ASCT.

In Turkey, finding a suitable related or an unrelated donor is a major handicap for allogeneic stem cell transplantation. In this retrospective study, we analyzed the results of patients treated with ASCT after HDARAC therapy in the first remission.

Materials and Methods

We retrospectively reviewed the data of 23 adult AML patients who have been diagnosed during 1998-2012. Patient data (diagnosis, FAB classification of the disease, age, gender, treatment protocols, the number of the chemotherapy cycles) were recruited from the archives of the hematology clinic (Table-1). All the patients were treated with 3+7 (ARA-C 100 mg/m^2 every 12 hours for 7 days and idarubicin 12 mg/m^2 for 3 days) as induction chemotherapy. After complete remission was achieved, consolidation chemotherapy consisted of high dose ARA-C (HDARAC, 3 gr/m^2 every 12 hours, on day 1, 3 and 5) was administered.

Table-1. Characteristics of the Patients.

Number of patients	23
Sex (female/male)	7 / 16
Number of patients in AML subtypes (M2, M4, M5, M6, M7, unclassified)	7, 7, 3, 1, 1, 4
Age (years)	43 (19 - 58)
Induction chemotherapy	7/3 ara-C, idarubicin
Consolidation chemotherapy	HDARAC
Mobilization regimen	HDARAC and G-CSF
Conditioning regimen	Busulfan and cyclophosphomide

Mobilization was performed by administrating HDARAC and granulocyte stimulating factor (G-CSF,10 µg/kg/day, filgrastim). Apheresis was initiated when the circulating CD34+ cell count was higher than 10 cells/L. All the patients were treated with Bu/Cy (Busulphan 0.8 mg/kg for 4 days, cyclophosphamide 60 mg/kg for 2 days) as conditioning regimen.

As supportive care, red blood cell and platelet concentrates were given to maintain the hemoglobulin level more than 8 gr/dL and platelet count more than 20X10^9/L at all chemotherapies. Ophthalmic steroids were given during HDARAC treatment. During the ASCT, anti-fungal, and antiviral prophylaxis was administered from day 1 until the neutrophil engraftment

was achieved. G-CSF was started on day 5 and continued until neutrophil engraftment was achieved.

Statistical analysis

Statistical analysis and survival rates were performed using the Prism 4.03 (GraphPad Software). The results were presented as median, maximum and minimum values. Values of *p* less than 0.05 were accepted as statistically significant.

Results

We retrospectively analyzed a total of 23 AML patients (7 female, 16 male) who were undergone ASCT. The median age of the patients was 43 years (range, 19-58). The FAB types of the patients were M2, M4, M5, M6, and M7 in 7, 7, 3, 1, 1 patient respectively. AML subtype could not be classified in 4 patients. Patients with M3 were excluded.

All the patients were treated with one cycle of 3+7 chemotherapy. Post remission, all patients were treated with HDARAC (median 2 cycles, range, 1-3 cycles) as consolidation chemotherapy. All the patients were mobilized with HDARAC and G-CSF. The median number of CD34+cells collected was $5.72X10^6$/kg (range, $2.57\text{-}39.89X10^6$/kg). The median time from diagnosis to ASCT was 6 months (range, 3-31 months). All the patients were in complete hematologic remission during mobilization and transplantation.

Neutrophil and thrombocyte engraftments were achieved in all patients. The median number of days to neutrophil and thrombocyte engraftments were 12 (range, 8-28 days) and 14 (range, 8-100 days) days, respectively. We did not document any death related directly to ASCT. 15 patients relapsed after transplantation. 13 of them died due to relapsed disease and one patient died due to reasons unrelated to primary disease. Remission was achieved again with re-induction chemotherapy, FLAG – ida (fludarabine 30 mg/m^2 and cytosine AraC 2 g/m^2 for 5 days, idarubicin 10 mg/m^2 for 3 days) in one patient who relapsed after ASCT.

The median follow up time after the first remission was 40 (range, 6-144 months) months. The median overall and disease free survival rates were 48 (range, 6-144) and 34 (range, 3-130) months, respectively. The overall survival rate at 144th month was 32.2 % (Figure-1); the overall survival rates of allogeneic stem cell transplantation in our institution were also shown for comparison) and the disease free survival rate was 27.3% at 130th month (Figure-2) (the disease free survival rates of allogeneic stem cell transplantation in our institution were also show for comparison).

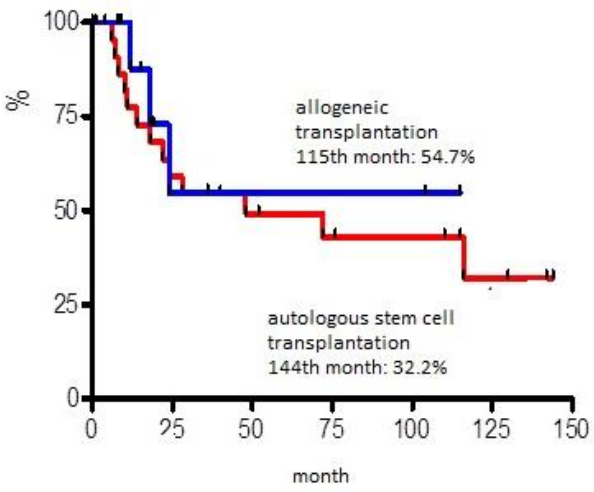

Figure-1. Overall survival rates in patients treated with ASCT and the comparison with allogeneic stem cell transplantation in the same institute.

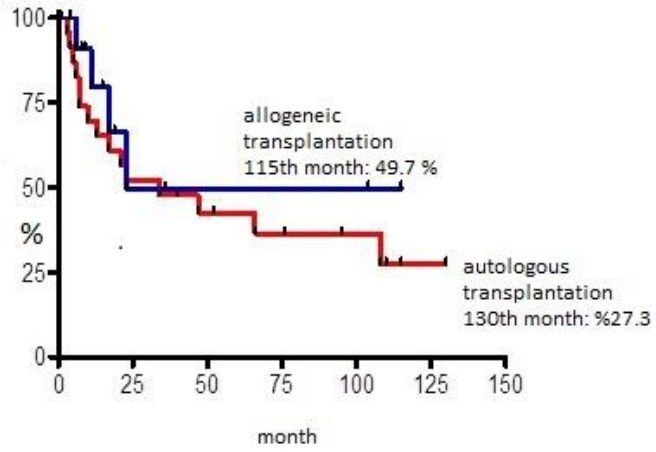

Figure-2. Disease-free survival rates in the patiens treated with ASCT and the comparison with allogeneic stem cell transplantation in the same institute.

Discussion

Although the role of ASCT in other hematologic malignancies especially in lymphoma and multiple myeloma is clear (12-16), its effectiveness in AML patients was not well established. In this retrospective study, we analyzed the results of 23 AML patients who received ACST. The median age was 43 years old in our study. In the literature the median age is between 37 and 53 years old which is compatible with our results (17-22).

Different types of chemotherapies were administered in the literature for remission induction (18,22,23). In this retrospective analysis, we treated all the patients with 3+7 chemotherapy. Post remission, median 2 cycles of HDARAC was given. In a prospective study, patients, in first complete remission after induction and first consolidation chemotherapies, were randomized to

receive one or two cycles of HDARAC. No benefit could be documented between two groups (21).

In our study, ASCTs were performed after a median of 6 months post transplantation. This is compatible with the literature (5,9). Peripheral or bone marrow source can be used for stem cell source. The source of stem cells changed from bone marrow to peripheral blood stem cell due to more rapid hematologic recovery and less infectious complications (22,24). A retrospective analysis of the EBMT registry did not show a difference in disease-free and overall survival between PBSC transplantation and bone marrow transplantation (24) but relapse rate is higher when compared with bone marrow source (22,25,26). This is probably due to leukemic cell contamination. In our study, peripheral blood stem cell transplantation was performed in all patients. The thrombocyte and neutrophil engraftment were achieved at median 12^{th} and 14^{th} day. Engraftment failure was not observed. These results were in accordance with the literature (17,22).

Overall survival and disease free survival were 48 and 34 months respectively in our study. In a prospective study by Zittoun et al. (27), the disease free survival rate was better than high dose chemotherapy with a similar overall survival rate. In another prospective randomized study by Tsimberidou et al. (28) that compared the outcomes of ASCT with peripheral stem cell source, allogeneic stem cell transplantation and HDARAC as post remission chemotherapy. In that study neither 3-year survival rates (58% versus 46%, p=0.08) nor failure free survival (42% versus 33%, p=0.83) were significantly different between HDARAC and ASCT groups. In the allogeneic stem cell transplanted group both the 3 year survival and failure free survival rates was 73%. The survival rates were comparable with ASCT group (28).

When relapse rates were compared between chemotherapy and ASCT groups, relapse rates were lower in transplanted patients in all risk groups. But relapse rates were higher in patients with unfavorable cytogenetic when compared to favorable one. This results probably indicates the patients who will most benefit from the ASCT. Relapse rate also was higher in patients with high levels of mobilized peripheral CD34 + cells (29,30).

Although the rate of relapses was lower and a better disease free survival rates were comfirmed in ASCT patients when compared with chemotherapy, the overall survival rates are not so encoraging (1,18,31). This result is probably because of transplanted related deaths and low rate of remission in patients who relapsed after ASCT. In addition, ASCT is a relatively safe procedure with a treatment related mortality of 6-15 % (22).

Conclusion

ASCT is a safe procedure with an advantage of better disease free survival, relapse rate and a low treatment related mortality. Although its effectiveness is mostly established in patients without poor risk factors, it should also be considered in all patients without a suitable donor.

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