Evaluation of Clinical Outcome and Mixed Chimerism Follow-up after Allogeneic Hematopoietic Stem Cell Transplantation in Hematological Malignancies

Hematolojik Malignitelerde Allojenik Hematopoetik Kök Hücre Transplantasyonu Sonrası Miks Kimerizmin Takibi ve Kliniğe Yansımlarının Değerlendirilmesi

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ABSTRACT

Objective: The level of donor-recipient chimerism is an established method to document donor engraftment. Allogeneic stem cell transplantation (ASCT) may result in mixed hematopoietic chimerism (MC), especially after reduced intensity conditioning regimens. Increasing MC levels in the post ASCT period may indicate disease relapse, graft failure, or rejection. In this study we aimed to study clinical outcome of mixed chimerism after ASCT in patients with hematological diseases.

Methods: The data of 335 patients whose ASCT were performed at our center between 2009 and 2019 and survived more than three months after transplantation were analyzed retrospectively.

Results: During follow up period 127 (43%) of 293 patients in full chimeric (FC) group and 11 (26.1%) of 42 patients in MC group died. 11 patients received donor lymphocyte infusions (DLI) after MC detected, 4 of them converted into FC. 10 mix chimeric patients converted into FC spontaneously. During follow up period 127 (43%) of 293 patients in FC group and 11 (26.1%) of 42 patients in MC group died. 11 patients received donor lymphocyte infusions (DLI) after MC detected, 4 of them converted into FC. 10 mix chimeric patients converted into FC spontaneously.

Conclusion: ASCT may result in MC especially after RIC regimens. MC does not always related with relapse risk and mix chimeric patients with malignant or benign hematological diseases can stay in remission for a long time.

Key Words: Chimerism, stem cell transplantation, allogeneic

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ÖZET

Amaç: Alıcının kimerizm düzeyinin takibi, donör engraftasyonunu tespit etmek için kullanılan bir yöntemdir. Allojenik kök hücre nakli (AKHN), özellikle düşük yoğunluklu hazırlıklardan sonra karışık tip kimerizme neden olabilir. AKHN sonrası karışık tip kimerizm seviyelerinin artması, hastalıktaki nüksü, greft yetmezliği veya reddini gösterebilir. Bu çalışmada, hematolojik malignite sebebiyle AKHN yapılan hastalarda, nakil sonrası karışık tip kimerizmin kliniğe yansımaları değerlendirilmiştir.

Yöntem: Merkezimizde 2009-2019 yılları arasında AKHN uygulanan ve transplantasyon sonrası sağkalımı üç ay üzerinde olan, 335 hastanın verileri retrospektif olarak incelendi.

Bulgular: Takipler sırasında, tam kimerik gruptan 293 hastanın 127’si (%43) ve karışık tip kimerizm grubundan ise 42 hastanın 11’i (%26.1) kaybedildi. Karışık tip kimerizm saptanan 11 hastaya donor lenfosit infüzyonu uygulandı, işlem sonrası 4 hasta tam kimerizme döndü. Yine karışık tip kimerizm tespit edilen 10 hasta ise kendiliğinden tam kimerizme dönüşmüştür. Takipler sırasında üç hastada donör ait hücre gözlenmedi (%0). Bu hastaların ikişi hala remisyonda takip edilmektedir. Karışık tip kimerizmde kalan 25’tir. Düşük yoğunluklu hazırlık 66 hastaya uygulandı ve bunların 10’unda (%15.1) karışık tip kimerizm tespit edildi. 269 hastaya miyelobaflatift kondisyon rejimi uygulandı ve bunların 32’sinin (%11.8) takiplerinde karışık tip kimerizm tespit edildi.

Sonuç: AKHN, özellikle düşük yoğunluklu hazırlıktan sonra karışık tip kimerizm ile sonuçlanabilir. Karışık tip kimerizm her zaman nüks riskiyle ilişkili değildir ve bu durumda uzun süre remisyonda kalabilirler.

Anahtar Sözcüklер: Kimerizm, kök hücre nakli, allojenik

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INTRODUCTION

Allogeneic stem cell transplantation (ASCT) is a potentially curative treatment used in a variety of benign and malignant hematologic diseases, solid tumors, neurological disorders, autoimmune diseases and immunodeficiencies. Early after ASCT, infections and graft-versus-host disease (GVHD) are major causes of death (1). The outcome of ASCT in malignant hematological diseases depends mainly on the immunologic graft-versus-leukemia effect of donor cell reactivity against host malignant cells whereas in benign hematological diseases it depends mainly on the replacement of donor’s cells instead of recipient’s cells and recovery of hematopoeisis.

Conditioning regimens for ASCT have variable intensity, toxicity and have been termed as myeloablative, reduced intensity, and non-myeloablative regimens. Myeloablative conditioning (MAC) regimen results in a long-lasting pancytopenia that is irreversible unless hematopoiesis is restored by infusion of donor stem cells. A non-myeloablative (NMA) regimen cause minimal cytopenia and may not require stem cell support. Reduced intensity conditioning (RIC) regimens cause cytopenias, which may be prolonged and require hematopoietic stem cell support (2–5). RIC regimens could decrease toxicity and related mortality (6). The approach has extended the scope of ASCT in patients who are not eligible candidates for standard ASCT because of their advanced age and/or comorbidities (6–9). 100 days after ASCT, relapse is the major cause of death and its incidence and outcome have not significantly improved over the last decades (1). A randomized study compared RIC and MAC conditioning regimens and found that RIC was associated with more relapse (10). The risk of relapse after RIC is 25–60% (11–16), and the median time to disease relapse is 3–7 months (17–20), therefore evaluating patients to detect relapse early in the post-transplant period is very important especially in patients who received NMA or RIC regimens. If relaps can be detected early after ASCT, treatments that can potentially prevent disease recurrence and improve survival such as maintenance regimens or donor lymphocyte infusions (DLI) should be considered (21).

The level of donor-recipient chimerism is an established method to document donor engraftment (22). ASCT may result in mixed hematopoietic chimerism (MC), especially after RIC regimens and after T-cell depletion that was not repeatable were discarded. Mixtures were assessed using allele-specific amplification (ASA) in order to obtain a single profile and to account for allelic drop-ins. Alleles were accepted as statistically significant.

MATERIALS and METHOD

Sample Preparation

In this study, the data of ≥18 years old patients whose ASCT were performed at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Bone Marrow Transplantation Center between 2009-2019 were analyzed retrospectively. Patients died due to transplant related mortality in the first 100 days after ASCT were excluded from the study.

Disease relapse was defined as morphologic, cytogenetic or radiologic evidence of disease demonstrating pre-transplant characteristics. Bone marrow biopsies were routinely performed at day 30. Donor-recipient chimerism levels were measured in the peripheral blood on day 30, 60, 90, and then every 3 months in the first two years and on every six months between 2nd and 5th year and annually after 5 years. Chimerism testing was performed more frequently in those with persistent MC. MC was defined as persistence of 5% to 95% residual recipient hematopoietic cells.
Median follow up of all patients was 33 months. During follow up period 127 (43%) of 293 patients in FC group and 11 (26.1%) of 42 patients in MC group died. 11 patients received DLI after MC detected, 4 of them converted into FC. 10 mix chimeric patients converted into FC spontaneously. In 3 patients no donor cell was observed in time (0%). 2 of them are still in remission. 25 patients remained mix chimeric during follow up period.

In our study, 66 patients received RIC regimen and 10 (15.1%) of them had MC during follow up period. 3 of these 10 mix chimeric patients who received RIC regimen had relapse disease and 2 of them died. 269 patients received MAC regimen and 32 (11.8%) of them had MC during follow up period. 14 of these 10 mix chimeric patients who received MAC regimen had relapse disease and 9 of them died. Lowest level of donor chimerism, time of first MC, time of lowest level of MC, relaps and mortality ratio, PFS and OS of mix chimeric patients were given in Table 2.

### DISCUSSION

The ability to detect relapse early in the post-transplant period is important to make treatment plan that can prevent disease recurrence and improve survival such as maintenance regimens or DLI. In addition determining chimerism may also be useful to monitor response to a DLI (29-31). There has been conflicting results regarding the correlation between disease relapse and chimerism levels after ASCT (31–34). In contrast to myeloablative transplants, RIC ASCT frequently results in varying degrees of MC (32, 33). Furthermore, MC may remain stable over time and may be together with prolonged remission, particularly in nonmalignant diseases, where MC may indicate a tolerant state associated with a low incidence of GvHD (36,37). Persisting MC was reported in 19 patients with hematological malignancies, with a median leukemia free survival of 12.5 years, and in patients with nonmalignant diseases, over a median period of 9.5 years after ASCT (38). In our study the mortality rate in MC patients was 26.1% and relapse rate was 40.4%. 59.5% of patients with MC is still in remission. The mortality rate in MC patients with hematological malignancy was 31.4 % and relapse rate was 45.7%. The relapse rate in MC patients with benign hematological diseases was 14.2% and no patient with benign hematological disease died. In the study conducted by Reshef et al, they found that early donor-recipient chimerism levels predicted relapse in ASCT recipients who received a peripheral blood stem-cell graft after a uniform RIC regimen. They found that the risk for relapse at 1 year in patients who have chimerism levels of 90, 95 and 100% are 52, 34 and 21% respectively (21). In our study, 66 patients received RIC regimen and 10 of them had MC during follow up period. 3 of these 10 mix chimeric patients had relapse disease and 2 of them died. In the study conducted by Levrat et al, MC remained stable in 72% (23/32) of mix chimeric patients alive at 10 years (25). In our study, 11 patients received DLI after MC detected, 4 of them converted into FC. 10 mix chimeric patients converted into FC spontaneously. In 3 patients no donor cell was observed in time (0%). 2 of them are still in remission. 25 patients remained mix chimeric during follow up period.

### Conflict of interest

No conflict of interest was declared by the authors.

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