

## Bölüm 24

# ALLOJENİK KÖK HÜCRE NAKLİ SONRASI NÜKS AKUT MYELOİD LÖSEMİDE TEDAVİ YAKLAŞIMLARI

Mehmet GÜNDÜZ<sup>1</sup>

Aysun ŞENTÜRK YIKILMAZ<sup>2</sup>

### GİRİŞ

Akut miyeloid lösemi (AML), Avustralya, Amerika Birleşik Devletleri ve Avrupa'daki yetişkinlerde (Pasquini&Wang, 2012) allojenik hemopoietik kök hücre naklinin (allo-HKHN) en yaygın nedenidir.

2011 yılı kayıt çalışmaları, donör kaynağına ve hastalık riskine bağlı olarak AML'de uzun süreli allo-HKHN sonrası sağkalımının % 20-50 (Gooley, Chien&Pergam, 2010) olduğunu bildirmektedir. Hastalık nüksü % 40'lar oranında allo-HKHN sonrası AML hastalarında, tedavi başarısızlığının ana nedeni olmaya devam etmektedir. İlk tam remisyonda (TR) AML için allo-HKHN sonrası kümülatif nüks oranı, orta sitogenetik risk AML için % 25-35 (Jourdan &ark, 2005) ve kötü sitogenetik risk AML için % 50-60'tır. (Chevallier &ark, 2012) .

Bir EBMT çalışmasında indirgenmiş yoğunluklu hazırlık rejimi (İYHR) ile yapılan allo-HKHN sonrası nüks AML hastalarında sağkalımı olumlu etkileyen 3 prognostik faktör saptanmıştır. Bunlar, nakil-nüks arası süresinin 5 aydan uzun olması, nüks sırasında kemik iliği blast sayısının <%27 olması ve nakil sonrası akut graft versus host hastalığı (GVHH) olmamasıdır. İki yıllık toplam sağkalım her 3 prognostik faktör varlığında %32, 2 prognostik varlığında %19, 0-1 prognostik varlığında oran %4 olarak bildirilmiştir. Bir uluslararası kan ve kemik iliği nakil araştırma (IBMTR) çalışmasında İYHR kullanılmasının sağkalımı olumlu etkilediği fakat yaş>41, kötü sitogenetik ve nüks sırasında aktif GVHH olmasının sağkalımı olumsuz etkileyen faktörler olduğu saptanmıştır. (Bejanyan&ark, 2015) Nükste, akut GVHH olmasının infeksiyöz komplikasyonları artırdığı ve hücre bazlı tedavilerin (ikinci allo nakil ve donör lenfosit infüzyonu) uygulama şansını azalttığı için sağkalımı olumsuz etkilediği düşünülmektedir.

<sup>1</sup> Uzm. Dr. Ankara Bilkent Şehir Hastanesi Hematoloji BD, drmgunduz02@gmail.com

<sup>2</sup> Uzm.Dr. Kahramanmaraş Necip Fazıl Kısakürek Şehir Hastanesi, Hematoloji, senturkaysun@gmail.com

ajanlar genellikle geri çekilir ve nadiren bunun kendisi büyük bir hastalık tepkisi doğuracaktır. Daha yaygın olarak, bazı sistemik tedavi ardından allojenik hücrel tedavi uygulanır. Sistemik tedavi, konvansiyonel kombinasyon indüksiyon kemoterapisinden yeni hedefli veya immünomodülatör ajanlara kadar uzanır. Hücrel tedavi genellikle DLI veya ikinci bir allojenik HKHN şeklindedir. En iyi prognoza sahip hastalar şaşırtıcı değildir, nükseden önce uzun bir remisyona giren ve hücrel tedavinin verilmesinden önce remisyona elde edebilenler şaşırtıcı değildir. Bu seçilmiş hasta alt grubunda, kalıcı remisyona oranlarının% 20–25'e yaklaşabileceği görülmektedir.

Daha yeni yaklaşımlar, hücrel tedavi olmadan GVL'yi geliştirebilecek gibi görünen lenalidomid ve GVHH'den kaçınmak için potansiyel olarak GVL'yi yönlendirebilecek CAR-T teknolojisi gibi ajanların kullanılmasını içerir. Bu yaklaşımların sonuçları merakla beklenmektedir. Önemli olarak, HKHN <yi takiben tekrarlayan AML'li hastalar için genel prognoz oldukça zayıf olduğu ve kalıcı remisyona olasılığının oldukça düşük olduğu göz önüne alındığında, palyatif önlemler uygundur ve HKHN <den sonra hastalığın erken ve agresif olarak tekrarlayan hastalara önerilmesi gerekir. Devam eden ve gelecekteki araştırmalar, HKHN 'den sonra hastalığın nükssetmesinin daha iyi önlenmesiyle sonuçlanacağını, etkili GVL'den daha iyi yararlanmanın yeni yollarını belirleyeceğini ve zaman içinde daha yüksek kalıcı remisyona ve iyileşme oranlarına yol açacağını umar.

## **KAYNAKLAR**

- Ballen KK, Koreth J, Chen YB, et al. Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. *Blood*. 2012;119:1972–80.
- Bar M, Sandmaier BM, Inamoto Y, et al. Donor lymphocyte infusion for relapsed hematological malignancies after allogeneic hematopoietic cell transplantation: prognostic relevance of the initial CD3+ T cell dose. *Biol Blood Marrow Transplant*. 2013;19:949–57.
- Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. *Biol Blood Marrow Transplant*. 2015 Mar;21(3):454-9).
- Blum W, Klisovic RB, Becker H, et al. Dose escalation of lenalidomide in relapsed or refractory acute leukemias. *J Clin Oncol*. 2010;28:4919–25.
- Bolanos-Meade J, Smith BD, Gore SD, et al. 5-azacytidine as salvage treatment in relapsed myeloid tumors after allogeneic bone marrow transplantation. *Biol Blood Marrow Transplant*. 2011;17:754–8.
- Brunner AM, Kim HT, Coughlin E, et al. Outcomes in patients age 70 or older undergoing allogeneic hematopoietic stem cell transplantation for hematologic malignancies. *Biol Blood Marrow Transplant*. 2013;19:1374–80.
- Brunstein CG, Fuchs EJ, Carter SL, et al. Alternative donor transplantation after reduced

- intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011;118:282–8.
- Chen YB, Spitzer TR. Current status of reduced-intensity allogeneic stem cell transplantation using alternative donors. *Leukemia*. 2008;22:31–41.
- Chevallier P, Prebet T, Pigneux A, et al. Influence of NPM1 and FLT3-ITD status on outcome in relapsed/refractory AML patients receiving salvage therapy including gemtuzumab ozogamicin. *Leukemia*. 2010;24:467–9.
- Chevallier P, Labopin M, Milpied N, et al.; ALWP of EBMT. Impact of cytogenetics risk on outcome after reduced intensity conditioning allo-SCT from an HLA-identical sibling for patients with AML in first CR: a report from the acute leukaemia working party of EBMT. *Bone Marrow Transplant* 2012;47:1442-1447.)
- Christopeit M, Kuss O, Finke J, et al. Second allograft for hematologic relapse of acute leukemia after first allogeneic stem-cell transplantation from related and unrelated donors: the role of donor change. *J Clin Oncol*. 2013;31:3259–71.
- Cortes JE, Kantarjian H, Foran JM, et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. *J Clin Oncol*. 2013;31:3681–7.
- Davids MS, Kim HT, Bachireddy P, et al.: Leukemia and Lymphoma Society Blood Cancer Research Partnership. Ipilimumab for patients with relapse after allogeneic transplantation. *N Engl J Med*. 2016;375:143–53.
- Devillier R, Crocchiolo R, Etienne A, et al. Outcome of relapse after allogeneic stem cell transplant in patients with acute myeloid leukaemia. *Leuk Lymphoma* 2013;54:1228-1234.
- Early AP, Preisler HD, Slocum H, et al. A pilot study of high-dose 1-beta-D-arabinofuranosylcytosine for acute leukemia and refractory lymphoma: clinical response and pharmacology. *Cancer Res*. 1982;42:1587–94.
- Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356:125–34.
- Faderl S, Wetzler M, Rizzieri D, et al. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I Trial. *J Clin Oncol*. 2012;30:2492–9
- Fathi AT, Chabner BA. FLT3 inhibition as therapy in acute myeloid leukemia: a record of trials and tribulations. *Oncologist*. 2011;16: 1162–74.
- Ford CD, Asch J, Konopa K, et al. CR with lenalidomide in del(5)(q13q33) AML relapsing after allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2010;45:403–4.
- Gale RE, Green C, Allen C, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood*. 2008;111:2776–84
- Gandhi V, Estey E, Keating MJ, et al. Chlorodeoxyadenosine and arabinosylcytosine in patients with acute myelogenous leukemia: pharmacokinetic, pharmacodynamic, and molecular interactions. *Blood*. 1996;87:256–64
- Goker H, Malkan UY, Demiroglu H, Buyukasik Y. Chimeric antigen receptor T cell treatment in hematologic malignancies. *Transfus Apher Sci*. 2016 Feb;54(1):35-40
- Goodyear O, Agathangelou A, Novitzky-Basso I, et al. Induction of a CD8+ T-cell response to the MAGE cancer testis antigen by combined treatment with azacitidine and sodium valproate in patients with acute myeloid leukemia and myelodysplasia. *Blood*. 2010;116:1908–18.

- Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med.* 2010;363:2091–101.
- Herzig RH, Wolff SN, Lazarus HM, et al. High-dose cytosine arabinoside therapy for refractory leukemia. *Blood.* 1983;62:361–9.
- Jabbour E, Giralt S, Kantarjian H, et al. Low-dose azacitidine after allogeneic stem cell transplantation for acute leukemia. *Cancer.* 2009;115:1899–905.
- Jeha S, Gandhi V, Chan KW, et al. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. *Blood.* 2004;103:784–9.
- Jensen MC, Riddell SR. Design and implementation of adoptive therapy with chimeric antigen receptor-modified T cells. *Immunol Rev.* 2014;257:127–44
- Jourdan E, Boiron J-M, Dastugue N, et al. Early allogeneic stem-cell transplantation for young adults with acute myeloblastic leukaemia in first complete remission: an intent-to-treat long-term analysis of the BGMT experience. *J Clin Oncol* 2005;23:7676–7684.
- Kantarjian H, Gandhi V, Cortes J, et al. Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. *Blood.* 2003;102:2379–86.
- Kurosawa S, Yamaguchi T, Miyawaki S, et al. Prognostic factors and outcomes of adult patients with acute myeloid leukemia after first relapse. *Haematologica.* 2010;95:1857–64.
- Leung AY, Tse E, Hwang YY, et al. Primary treatment of leukemia relapses after allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning second transplantation from the original donor. *Am J Hematol.* 2013;88:485–91.
- Levine JE, Braun T, Penza SL, et al. Prospective trial of chemotherapy and donor lymphocyte infusions for relapse of advanced myeloid malignancies after allogeneic stem-cell transplantation. *J Clin Oncol* 2002;20:405–412.
- Levis MJ, Perl AE, Dombret H, et al.: Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia After Second-Line Chemotherapy or Hematopoietic Stem Cell Transplantation. *Blood (ASH Annual Meeting Abstracts)* 120:Abstract 673, 2012.
- Loren AW, Porter DL. Donor leukocyte infusions for the treatment of relapsed acute leukemia after allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2008;41:483–93.
- Lubbert M, Bertz H, Wasch R, et al. Efficacy of a 3-day, low-dose treatment with 5-azacytidine followed by donor lymphocyte infusions in older patients with acute myeloid leukemia or chronic myelomonocytic leukemia relapsed after allografting. *Bone Marrow Transplant.* 2010;45:627–32.
- Metzelder S, Wang Y, Wollmer E, et al. Compassionate use of sorafenib in FLT3-ITD-positive acute myeloid leukemia: sustained regression before and after allogeneic stem cell transplantation. *Blood.* 2009;113:6567–71.
- Metzelder SK, Schroeder T, Finck A, et al. High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. *Leukemia.* 2012;26:2353–9.
- Momparler RL. A model for the chemotherapy of acute leukemia with 1-beta-D-arabinofuranosylcytosine. *Cancer Res.* 1974;34:1775–87.
- Oran B, de Lima M. Prevention and treatment of acute myeloid leukemia relapse after allogeneic stem cell transplantation. *Curr Opin Hematol.* 2011;18:388–94.

- Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2012. Available at <http://www.cibmtr.org>. Accessed 10 April 2013.
- Pilorge S, Rigaudeau S, Rabian F, et al. (2014) Fractionated gemtuzumab ozogamicin and standard dose cytarabine produced prolonged second remissions in patients over the age of 55 years with acute myeloid leukemia in late first relapse. *Am J Hematol* 89(4):399–403. doi:10.1002/ajh.23653
- Pinto A, Maio M, Attadia V, et al. Modulation of HLA-DR antigens expression in human myeloid leukaemia cells by cytarabine and 5-aza-2'-deoxycytidine. *Lancet* 1984;2:867–8.
- Pizzitola I, et al. Chimeric antigen receptors against CD33/CD123 antigens efficiently target primary acute myeloid leukemia cells in vivo. *Leukemia* 2014; 28:1596–1605.
- Rautenberg C, Nachtkamp K, Dienst A, et al. Sorafenib and azacitidine as salvage therapy for relapse of FLT3-ITD mutated AML after allo-SCT. *Eur J Haematol*. 2017 Apr;98(4):348-354
- Reese ND, Schiller GJ. High-dose cytarabine (HD araC) in the treatment of leukemias: a review. *Curr Hematol Malignancy Rep*. 2013;8:141–8.
- Ritchie, DS, Neeson, PJ, Khot, A. Persistence and efficacy of second generation CAR T cell against the LeY antigen in acute myeloid leukemia. *Mol Ther* 2013; 21: 2122–2129.
- Robak T, Wrzesien-Kus A, Lech-Maranda E, et al. Combination regimen of cladribine (2-chlorodeoxyadenosine), cytarabine and G-CSF (CLAG) as induction therapy for patients with relapsed or refractory acute myeloid leukemia. *Leuk Lymphoma*. 2000;39:121–9.
- Schmid C, Labopin M, Nagler A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol*. 2007;25:4938–45.
- Schroeder T, Frobels J, Cadeddu RP, et al. Salvage therapy with azacitidine increases regulatory T cells in peripheral blood of patients with AML or MDS and early relapse after allogeneic blood stem cell transplantation. *Leukemia*. 2013;27:1910–3.
- Soiffer RJ. Donor lymphocyte infusions for acute myeloid leukaemia. *Best Pract Res Clin Haematol*. 2008;21:455–66.
- Sorrer ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306:1874–83.
- Stone RM, Moser B, Sanford B, et al. (2011) High dose cytarabine plus gemtuzumab ozogamicin for patients with relapsed or refractory acute myeloid leukemia: cancer and leukemia group B study 19902. *Leuk Res* 35(3):329–333
- Tachibana T, Tanaka M, Takasaki H, et al. (2011) Successful treatment with gemtuzumab ozogamicin and donor lymphocyte infusion for acute myeloid leukemia relapsing after allogeneic stem cell transplantation. *Int J Hematol* 94(6):580–582.
- Tasian SK. Acute myeloid leukemia chimeric antigen receptor T-cell immunotherapy: how far up the road have we traveled? *Ther Adv Hematol*. 2018 Jun;9(6):135-148.
- Tse E, Leung AY, Sim J, et al. Clofarabine and high-dose cytosine arabinoside in the treatment of refractory or relapsed acute myeloid leukaemia. *Ann Hematol*. 2011;90:1277–81.

- Van den Brink MR, Porter DL, Giralt S, et al. Relapse after allogeneic hematopoietic cell therapy. *Biol Blood Marrow Transplant.* 2010;16:S138–45
- Van der Velden VHJ, te Marvelde JG, Hoogeveen PG, et al. (2001) Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. *Blood* 97(10):3197–3204. doi:10.1182/blood.V97.10.3197
- Wang, QS, Wang, Y, Lv, HY. Treatment of CD33-directed chimeric antigen receptor-modified T cells in one patient with relapsed and refractory acute myeloid leukemia. *Mol Ther* 2015; 23: 184–191.
- Winkler J, Rech D, Kallert S, et al. Sorafenib induces sustained molecular remission in FLT3-ITD positive AML with relapse after second allogeneic stem cell transplantation without exacerbation of acute GVHD: a case report. *Leuk Res.* 2010;34:e270–2.
- Xie KC, Plunkett W. Deoxynucleotide pool depletion and sustained inhibition of ribonucleotide reductase and DNA synthesis after treatment of human lymphoblastoid cells with 2-chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl) adenine. *Cancer Res.* 1996;56:3030–7.