Comment on Russo et al, page 247

NK cell destiny after haploSCT with PT-Cy

Amnon Peled[1] and Arnon Nagler[2] | [1]Hadassah University Hospital; [2]Tel Aviv University

In this issue of *Blood*, Russo et al provide important insights on the effect of posttransplantation cyclophosphamide (PT-Cy) on natural killer (NK) cell recovery and function after haploidentical allogeneic stem cell transplantation (haploSCT).[1]

Allogeneic hematopoietic stem cell transplantation is a potentially curative procedure for a variety of hematologic malignancies, including acute leukemia and myeloproliferative disorders. For patients who lack an HLA-matched sibling donor, transplantation from a haploidentical donor is an emerging alternative. HaploSCT has a number of advantages, including unlimited donor availability and accessibility of posttransplant donor-derived immune cells. However, T cell–depleted haploSCT is associated with delayed immune reconstitution as a result of depletion of immune cells, which leads to an increased transplant-related mortality mainly because of infections. In addition, reduced graft-versus-leukemia effect resulting from heavy immunosuppression may lead to a high relapse rate. Some of these limitations are overcome by leaving the T cells in the graft (the so-called non-T–depleted haploidentical transplantation), which has yielded encouraging results. The T-replete haploSCTs are being performed with either anti-thymocyte globulin or more recently PT-Cy. In several recent nonrandomized studies, survival outcomes after haploSCT with PT-Cy have been comparable to those of transplantations from unrelated and even sibling donors. However, further prospective randomized con-trolled trials are needed to establish the efficacy and safety of this procedure.[2-5]

In the Russo et al study, 3 days after the infusion of the unmanipulated stem cell graft, donor mature NK cells robustly proliferated. As previously described for T lymphocytes, NK cell proliferation was completely abrogated by day 8 after PT-Cy, suggesting selective elimination of cycling NK cells. Importantly, donor NK cells harvested from patients at days 15 and 30 after haploSCT had a less mature phenotype and expressed the NKG2A and CD62L molecules. These data suggest that NK cell recovery occurs through maturation of NK progenitors in the bone marrow rather than by homeostatic expansion of mature graft NK cells. The phenotypic recovery of the NK cell repertoire was found to be a long process taking up to 1 year after the haploidentical transplantation with PT-Cy. Moreover, the recovery was dependent on interleukin-15 (IL-15) because systemic levels of IL-15 rose immediately after graft infusion and displayed a direct correlation with the number of NK cells reconstituting thereafter. IL-15 has previously been reported to be a key cytokine for in vivo expansion of NK cells.[6]

It has been reported that donor-recipient KIR ligand mismatches can unleash reconstituting donor NK cells against residual tumor cells.[7,8] After transplantation, alloreactive single KIR+ NK cells had a high level of proliferation, which was completely abrogated in response to PT-Cy. Subsequently, single KIR+ NK cells present in the graft became undetectable in the peripheral blood (PB) of the patients who had received a transplant at day 30.

To determine antileukemic potential, NK cells were purified from patients at day 30 after transplant and compared for their in vitro killing activity with their counterparts from the corresponding donor PB NK cells. Patients' NK cells displayed impaired killing of the OCI/AML03 cell line and of primary acute myeloid leukemia blasts. This suggests that the immature KIR+–depleted NK cells reconstituting the blood after PT-Cy display an impaired antileukemic potential compared with their mature donor counterparts.

The proportion of mature alloreactive NK cells before transplant and after haploSCT with PT-Cy may have a clinically relevant role in determining transplantation outcome. In a cohort of 99 consecutive patients who received myeloablative chemotherapy-based conditioning and haploSCT followed by PT-Cy, NK cell alloreactivity (observed in 41% of the patients) before transplant did not significantly affect any of the major transplantation outcomes, including graft-versus-host disease, relapse incidence, and survival. In contrast, in univariable analysis, low expression of CD62L and high expression of KIRs on NK cells at day 30 after transplant significantly correlated with lower incidence of relapse. Moreover, high expression of KIRs on NK cells at day 30 also displayed a significant correlation with higher progression-free survival.

This in vitro and in vivo finding suggests that KIR expression on NK cells might represent a clinically relevant mean for the functional competence of reconstituting NK cells in preventing leukemic recurrence. More importantly, the described elimination of the donor NK cells early after Cy administration in conjunction with the slow recovery (up to 1 year) of recipient NK cells that express immature phenotype and have impaired killing capabilities may explain the high incidence of leukemic relapse that was initially reported with the PT-Cy technique[9] and the susceptibility to viral infections.[10] Furthermore, these results imply that infusion of donor alloreactive NK cells into posttransplant Cy-treated patients in the face of high levels of serum IL-15, which have been demonstrated to provide a favorable environment for adoptive infusion of mature donor NK cells, might have beneficial outcomes in reducing both relapse incidence and viral infections.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ∎

REFERENCES

1. Russo A, Oliveira G, Berglund S, et al. NK cell recovery after haploidentical HSCT with post-transplant cyclophosphamide: dynamics and clinical implications. *Blood*. 2018;131(2):247-262.

2. Mancusi A, Ruggeri L, Velardi A. Haploidentical hematopoietic transplantation

for the cure of leukemia: from its biology to clinical translation. *Blood.* 2016;128(23): 2616-2623.

3. Farhadfar N, Hogan WJ. Overview of the progress on haploidentical hematopoietic transplantation. *World J Transplant.* 2016;6(4): 665-674.

4. Atilla E, Atilla PA, Bozdağ SC, Demirer T. A review of infectious complications after haploidentical hematopoietic stem cell transplantations. *Infection.* 2017;45(4):403-411.

5. Lee CJ, Savani BN, Mohty M, et al. Haploidentical hematopoietic cell transplantation for adult acute myeloid leukemia: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica.* 2017; 102(11):1810-1822.

6. Miller JS, Soignier Y, Panoskaltsis-Mortari A, et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. *Blood.* 2005;105(8): 3051-3057.

7. Locatelli F, Pende D, Mingari MC, et al. Cellular and molecular basis of haploidentical hematopoietic stem cell transplantation in the successful treatment of high-risk leukemias: role of alloreactive NK cells. *Front Immunol.* 2013;4:15.

8. Ruggeri L, Mancusi A, Capanni M, et al. Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value. *Blood.* 2007; 110(1):433-440.

9. Brunstein CG, Fuchs EJ, Carter SL, et al; Blood and Marrow Transplant Clinical Trials Network. 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(2): 282-288.

10. Crocchiolo R, Bramanti S, Vai A, et al. Infections after T-replete haploidentical transplantation and high-dose cyclophosphamide as graft-versus-host disease prophylaxis. *Transpl Infect Dis.* 2015;17(2):242-249.