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Donor-Derived Cytokine-Induced Killer Cells after Nonmyeloablative Transplant for Myeloid Neoplasms

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Cytokine-induced killer (CIK) cells are a heterogenous population of $CD3^+CD56^+$natural killer (NK)-like T lymphocytes that are generated ex vivo by stimulating peripheral blood lymphocytes with cytokines (anti-CD3, IL-2, and IFN-γ). These innate immune cells exhibit antitumor cytotoxicity in a non-MHC restricted manner and primarily recognize tumors through the NK group 2, member D (NKG2D) receptor. CIK cells are being studied for adoptive cell therapy for solid tumors and hematologic malignancies [1]. In patients with hematologic neoplasms who relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT), donor CIK cell infusions were safe with a low incidence of acute graft-versus-host disease (GVHD) [2,3]. Interestingly, 2 patients with mixed donor chimerisms converted to full donor chimerism after CIK infusions and experienced a complete response [4].

In this issue, Narayan et al. [5] report the results of a phase II study of CIK cell therapy after nonmyeloablative (NMA) allo-HSCT for myeloid neoplasms. Eligible diseases included myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), or therapy-related myeloid neoplasms. In their single-center, non-randomized, prospective trial, the authors sought to evaluate the effect of a single dose of donor-derived CIK cells after NMA allo-HSCT. They hypothesized that post-transplant consolidation with donor-derived CIK cells would be safe and promote early donor chimerism. After NMA conditioning with total lymphoid irradiation and antithymocyte globulin, patients underwent an allo-HSCT (unrelated or related) and were subsequently treated with a single dose of CIK cells on days +21 to +35 at a target dose of 1×10^8 $CD3^+$ cells/recipient kg.

CIK cells were infused in 31 of 44 patients treated on study. Outcomes were compared with a retrospective historical cohort of 100 patients. The authors found no significant difference in achieving full donor chimerism on day +90 in the CIK recipients compared with historical control subjects (19% versus 27%, respectively; $P = .482$). Similarly, there was no significant difference in the 2-year relapse-free survival, event-free survival, nonrelapse mortality, or overall survival between the CIK recipients and historical control subjects. There was no significant difference in grades II to IV acute GVHD or chronic GVHD between the study cohort and the historical cohort; however, there was a significant increase in both 100-day and 1-year cumulative incidence of grades III to IV acute GVHD in the study cohort ($P < .001$). The authors comment that given the small sample size and number of events the significance should be interpreted with caution. Prior therapy with cytoreductive induction–type chemotherapy was associated with increased relapse-free survival (hazard ratio [HR], .233; $P = .049$). The presence of monosomal or complex karyotype and having MPN or MPN/MDS overlap compared with MDS were both less favorable for relapse-free survival (HRs, 2.846 [$P = .00884$] and 2.971 [$P = .044$], respectively). On univariate analysis, the only pretransplant variable that significantly affected OS was the presence of monosomal or complex karyotype (HR, 3.075; $P = .009$). On multivariate analysis, however, they did not identify factors that were significantly associated with survival.

This is the first report of post-transplant consolidation with allogeneic CIK cells for myeloid malignancies after NMA conditioning. The use of reduced-intensity and NMA conditioning regimens has opened the door for treating elderly patients and those with comorbid medical conditions with potentially curative allo-HSCT. There are 2 purposes of conditioning before HSCT: cytoreduction for tumor control and immunosuppression to overcome host rejection of the graft. Thus, the potential risks of NMA are graft rejection and disease relapse. Although conditioning regimens and outcomes vary between NMA protocols, delayed full donor chimerisms and graft rejection are more common in NMA for allo-HSCT [6]. Mixed chimerism or delayed full donor chimerism is associated with higher risk of relapse [7,8]. Activated donor NK cells have been shown to improve engraftment and promote early full donor chimerism [9,10]. Here, the authors hypothesized that activated CIK cells given 21 to 35 days after transplant would similarly improve rates of early full donor chimerism. In this setting, they were not able to show an improvement in engraftment. Although

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CIK cells have many similarities with NK cells, they lack many of the NK cell–specific KIR inhibitory receptors that are responsible for NK licensing and alloreactivity. KIR receptor/ligand mismatch in the early post-transplant period is believed to be responsible for NK cell antileukemia effect, decreased rates of GVHD, and improved engraftment after haploidentical or KIR mismatched HSCT. Moreover, earlier administration of NK cells both before and 1 week after stem cell infusion may contribute to the early antitumor activity and reduction of recipient T cells responsible for delayed engraftment [11]. The antithymocyte globulin–based conditioning regimen in this study limits the use of CIK infusion before stem cell infusion or in the very early post-transplant period and may be a limitation to this approach.

The authors suggest one way to improve CIK cell potency is to generate CIK cells modified with chimeric antigen receptors (CARs) against myeloid antigens. Although CAR CIK cells against a variety of tumor antigens are being studied, the myeloid antigens currently targeted are also present on normal myeloid precursors, which make them difficult to use for post-transplant consolidation without affecting graft function. It is also important to consider the heterogenous composition of CIK, which includes T cells, NKT cells, and NK cells. As we learn more about CAR T cell efficacy in the clinic, it is becoming apparent that the cell composition and T cell phenotype of the final CAR T cell product efficacy and persistence. Given the 2- to 3-week culture with cytokines necessary to generate CIK cells, it will be important to compare the phenotype and exhaustion of these products with traditional CAR T cells.

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