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The Bottom Line

Donor Lymphocyte Infusions versus Cytokine-Induced Killer Cells for Hematologic Malignancies after Transplantation

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For 3 decades, donor lymphocyte infusion (DLI) has been used to exploit the graft- versus-leukemia (GVL) effect after post-transplantation relapse and, more recently, as preemptive therapy to prevent relapse after hematopoietic stem cell transplantation (HSCT) [1–3]. The success of DLI has been most pronounced in treating chronic myelogenous leukemia (CML). Studies have shown >70% complete cytogenetic remission (CR) in patients with CML treated with DLI after relapse, particularly patients in molecular/cytogenetic relapse and those in the chronic phase of hematologic relapse [4]. The response rates are less robust in the acute leukemias, with remission rates of 15% to 42% [5]. The benefits of the GVL effect must also be weighed against the risk of graft-versus-host disease GVHD, which is reported in 40% to 50% of patients receiving DLI. Strategies to improve the efficacy and decrease toxicity of DLI include alternative dosing strategies, risk-adapted use, the addition of checkpoint inhibitors, and ex vivo activation of DLI effector cells with cytokines. The latter approach uses IFN-γ, IL-2, and anti-CD3 to generate cytokine-induced killer cells (CIKs). These cells primarily express both CD3 and CD56 and recognize tumor targets in a non-MHC-restricted manner via the NKG2D receptor, making them natural killer-like T cells.

In this issue of the *Journal*, the authors compare the use of DLI versus CIK cells after hematopoietic stem cell transplantation for hematologic malignancies including CML, acute myelogenous leukemia, acute lymphocytic leukemia, biphenotypic leukemia, and T cell non-Hodgkin lymphoma [6]. Patients were treated after either molecular or morphological disease recurrence or prophylactically in those with refractory disease at the time of transplantation. In this nonrandomized study, patients were treated with DLI between 2001 and 2011 or DLI or CIK for the remainder of the study with preferential treatment with CIK if a manufacturing slot was available. For DLI, cell dose was determined by donor type and degree of HLA matching, with the lowest dose given to haploidentical donors (range, .1 to 1×10^6 cells/kg). For CIK, the starting dose was 1×10^6 cells/kg regardless of donor type, with the ability to escalate dose for subsequent infusions if there was no evidence of GVHD (range, 1×10^6 cells/kg to 1×10^8 cells/kg). Therapeutic cellular infusions were stopped after complete molecular remission (CMR) was achieved or for greater than grade I acute GVHD (aGVHD).

Overall, 16 of 55 patients (29%) who received DLI achieved CR compared to 16 of 36 (53%) of patients who received CIK cell therapy. All patients with frank hematologic relapse at the time of cell-based therapy died from their disease. The 6-month overall survival of patients who received preemptive (molecular relapse and prophylactic therapy) DLI and CIK therapy was 57% and 77%, respectively. There was a trend toward a benefit of CIK therapy on both univariate and multivariate analysis, but the results were not significant ($P = .122$ and .055, respectively). However, the cumulative incidence of relapse was significantly lower in patients who received CIK therapy (22%) versus those who received DLI (55%) ($P = .012$). The benefit of CIK therapy for prevention of relapse was most pronounced in patients who received prophylactic treatment, with a relapse incidence of 18% following CIK therapy versus 78% after DLI ($P = .006$). There was no difference in the cumulative incidence of aGVHD (grade II-IV) between the 2 groups, despite the significantly higher cumulative T cell dose in patients receiving CIK cells (median, 6.5×10^6/kg versus 1.1×10^6/kg; $P < .001$).

In this retrospective study, the authors were not clearly able to show a benefit for CIK cell therapy compared with traditional DLI, although there was a trend toward improved outcomes with CIK therapy for molecular relapse or prophylactic treatment. Without cytoreductive chemotherapy, the use of DLI in acute leukemias has not historically been shown to be effective. This is likely secondary to high disease burden, rapid rate of cell division, and immune escape mechanisms in these malignancies. With this in mind, it is not surprising that all patients in this study with morphological relapse at the time of cell infusion died of their disease. Studies using CIK cells with the addition of chemotherapy after relapsed acute leukemia are ongoing, and it will be interesting to compare these results with historical data using DLI in this setting.

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In this study, CIK cell therapy was given earlier after transplantation compared with DLI and was associated with improved T cell recovery; however, the authors do not comment on the effect of viral reactivation in these patients. In the DLI group, 1 patient died of Epstein-Barr virus (EBV) encephalopathy, and 1 patient died of adenovirus and human herpes virus 6 infection. In the CIK group, 1 patient died from pneumocystis pneumonia, 1 patient died of respiratory syncytial virus pneumonia, and 3 patients had organ impairment from a viral infection (adenovirus, cytomegalovirus, and EBV). From this description, it does not appear that there were any differences in morbidity and mortality related to viral infections with improved T cell reconstitution after CIK cell therapy. The earliest administration of immune therapy in this cohort was between days +30 to +40 in patients being treated prophylactically. The potential benefits of adoptive immune cell therapy for post-transplantation viral reactivation are more likely to be seen in the early post-transplantation period when patients are at high risk for infectious complications. Unselected donor leukocytes have been used to successfully treat cytomegalovirus, adenovirus, and EBV lymphoproliferative disease post-transplantation, and it is possible that with a larger cohort of prophylactic patients, an infectious disease benefit of DLI or CIK therapy may be seen [7,8].

Many questions remain regarding the ideal culturing conditions, tumor types, dosing strategy and concurrent therapies for CIK cell therapy. With the rise of potent, targeted cell-based therapies being developed to treat relapsed hematologic malignancies, the use of this type of unselected therapy may become outpaced in this setting.

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