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EDITORIALS

Natural Killer Cell Consolidation for Acute Myelogenous Leukemia: A Cell Therapy Ready for Prime Time?

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Advances in the treatment of children and adults with acute myeloid leukemia (AML) have been hindered by several factors. There is a paucity of new and effective chemotherapeutic or biologic agents directed against this disease.

Current cytotoxic therapies have reached the limit of both myelosuppression and safety. Understanding the appropriate subsets of AML that may benefit from matched related or unrelated donor allogeneic hematopoietic cell transplantation (alloHCT) is evolving, with application of HCT limited by concerns of toxicity and efficacy.

There is a desperate need for novel treatment approaches. Cell-based therapies represent an area of exciting scientific and clinical development.

Because of the relatively poor outcomes of patients treated only with chemotherapy, autologous HCT and alloHCT have been used as consolidation therapy for patients with AML. Although autologous HCT outcomes match those achieved with chemotherapy, most studies comparing chemotherapy with alloHCT demonstrate reductions in leukemia relapse and improved disease-free survival for patients undergoing alloHCT.

Both autologous HCT and alloHCT may exert leukemia control through the high-dose conditioning regimen, but in alloHCT, the focus is on the potential of the procedure to provide immune-based eradication of malignant cells, known as the graft-versus-leukemia (GVL) effect.

Considering that natural killer (NK) cells are one of the first cells to recover after alloHCT, these cells have been implicated in GVL reactions.

NK cells express a diverse array of receptors used to distinguish between normal and transformed cells.
One family of receptors displayed by NK cells is the killer immunoglobulin receptors (KIR). KIRs recognize polymorphic determinates of major histocompatibility class (MHC) I. By binding to self-MHC and transducing inhibitory signals, these receptors play a major role in the self-tolerance of NK cells.

In the setting of alloHCT, KIR receptors on donor NK cells may not recognize recipient MHC class I (because of difference between donor and recipient MHC class I).
This situation potentially would leave the NK cell unrestrained and more effective at mediating GVL.
Clinical transplant trials strongly suggest that this mechanism, known as NK cell alloreactivity, plays a role in post-transplant GVL responses in AML.
This effect may require profound host lymphopenia and a T-cell depleted graft, because KIR mismatches did not provide a benefit in retrospective analysis, whereas a subsequent retrospective study was able to detect a positive effect of KIR mismatching in the setting of in vivo T-cell depletion.

A major barrier to the success of alloHCT is the toxicity associated with the procedure.

Many variables influence treatment-related mortality, including host factors (age, prior treatment, performance status) and transplantation characteristics (conditioning regimen, MHC disparity between donor and recipient, stem-cell source, and so on).

Despite selecting patients with favorable characteristics, treatment-associated mortality is substantial after alloHCT, especially in the matched unrelated donor or haploidentical donor setting.

An ideal transplantation approach would be one that preserves GVL reactions while maintaining patient safety.

In this issue of *Journal of Clinical Oncology*, Rubnitz et al report on a pilot study to test the safety and feasibility of haploidentical NK cell infusions, without concomitant hematopoietic stem-cell infusion or attempt to establish donor hematopoiesis, in 10 children with AML in remission.

The patients included on this protocol had standard- or intermediate-risk AML in first complete remission, a group of patients for whom standard therapy of at least a subset would include alloHCT were a matched sibling donor available.
Patients were first treated with four to five cycles of standard AML therapy.
After this, a haploidentical parent or sibling was selected as an NK cell donor, based on the presence of KIR mismatch between donor and recipient (except in one instance).

Donor cells were collected by leukophoresis, purified by CD3 depletion to remove T cells, and followed by CD56 selection to purify NK cells, producing a highly NK cell–enriched cell product.

These NK cells were infused after immunosuppressive, but not myeloablative, conditioning to provide a lymphopenic environment in the host.

After the cell infusion, patients were treated briefly with low-dose interleukin 2 (IL-2) to support in vivo NK expansion. The authors demonstrate a transient expansion of donor-derived cytotoxic NK cells in the peripheral blood of all recipients.

The conditioning regimen, cell infusion, and IL-2 administration were remarkably well tolerated, with minimal toxicity and hospitalization.

Specifically, there was indirect evidence of transient NK-induced suppression of recipient myelopoiesis in only one patient and no graft-versus-host disease.

This study builds on the findings of the Miller et al study, which used a similar approach (chemotherapy followed by NK cell infusion) to demonstrate that haploidentical NK cells induce remissions in a proportion of patients with chemotherapy-refractory AML.

Similar to Rubnitz et al, Miller et al showed transient donor NK cell engraftment and cytotoxicity and demonstrated that this correlated with a surge of systemic IL-15—a critical survival factor for NK cells. Donor NK cell expansion was correlated with the likelihood of hematologic remission.

Rubnitz et al have made subtle but significant refinements in this approach, including the use of less-intensive chemotherapy, a purified NK cell product, and lower doses of IL-2. Rubnitz et al also omitted an overnight culture and NK activation step performed by Miller et al, and instead infused freshly isolated cells.

Although these modifications seem to have resulted in less toxicity, it is important to note that the patient population in these two studies differed considerably (children in remission in the Rubnitz et al study *v* adults not in remission in the Miller et al study).

As is the nature of pilot studies, they often raise more questions than answers.

First is the question of efficacy. Notably, all patients in the Rubnitz et al study are alive and in remission at nearly 3 years. Did the NK therapy contribute to efficacy? Although encouraging, the authors show appropriate restraint in interpreting the outcome data from this small cohort of patients and currently are performing phase II studies.

Second is the question of cost. We approximate the cost of such a therapy to be $10,000 to $12,000 per patient, which, although expensive, compares favorably to the cost of alloHCT or many recently approved anticancer therapies.

Last is the question of "exportability." Although only facilities capable of good manufacturing practices would be able to deliver such a therapy, the cell manufacturing described here would be highly exportable compared with other cell manufacturing protocols.

Whatever subsequent studies show, it is clear that Rubnitz et al should be commended. This study could have far-reaching implications in cellular therapy for patients with AML.

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