SPECIAL REPORT

Adoptive immunotherapy for myeloid malignancies

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In allogeneic stem cell transplantation (allo-SCT), much of the anti-tumor effect is derived from a graft versus tumor (GVT) response that is dependent on donor cell engraftment. In order to attain engraftment large doses of chemotherapy are administered to suppress the host's immune system. Toxicities from allo-SCT are derived from these chemotherapy doses by causing myelosuppression and the resultant bleeding and infection risk that comes with it, as well as the threat that engrafted donor immune cells recognize normal rather than malignant cells, causing graft versus host disease (GVHD) rather than GVT. Previous work has shown the infusion of allogeneic matched and haploidentical peripheral blood stem cells with minimal conditioning can result in durable responses for patients with refractory leukemia/lymphoma in the absence of engraftment.^{1–4} Furthermore, responders to therapy demonstrated a robust cytokine release syndrome that is similar to that seen in chimeric antigen receptor-modified T cells in its involvement of the release of interferon- γ (IFN- α) and interleukin-6 (IL-6).^{2,5} Based on the loss of chimerism in responders, we hypothesize that the mechanism of action behind response is via the generation of a host versus tumor and not a graft versus tumor response.

Our current cellular therapy protocol seeks to further develop cellular infusion as a form of immunotherapy for refractory hematological malignancies.⁶ Patients are enrolled in an already FDA and institutional review board-approved trial that utilizes peripheral blood mononuclear cells (PBMNC) collected from human leukocyte antigen-haploidentical donors. The PBMNC are then infused unmanipulated and without any conditioning regimen to patients with refractory leukemia and lymphoma to create an allogeneic rejection effect that has previously been described in a mouse chimeric model.^{7–10} We hypothesize that elimination of the conditioning regimen will decrease the likelihood of engraftment while increasing the host's ability to generate an immunological response against the donor cells. The primary objective is the overall response rate, while secondary objectives seek to determine the underlying mechanism of action in terms of effector cell populations and how these effects can be further augmented.

Thus far, three patients have been enrolled in our current protocol. Two out of three patients have developed the cytokine release syndrome with hyperpyrexia as well as elevations in IFN- α , IL-6 and IL-10 following infusion. These two patients saw an increase in their absolute neutrophil counts that was transient in nature. No signs of GVHD were observed and detectable chimerism (level of detection up to <2%) was lost in all patients by day 7 post infusion. CD3+ cell dose appears to be important for response as patients 1 and 2

received 1×10^8 CD3+ cells/kg while patient 3 received 2×10^8 CD3+ cells/kg. This third patient developed a pronounced cytokine release syndrome followed by a decrease in peripheral and bone marrow blast counts post infusion compared to more modest effects seen in patients 1 and 2. Patient 3 remains alive with a leukemic marrow but with a prolonged decrease in peripheral circulating blast counts now 4 months post cellular infusion.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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