Non-technical Abstract

Numerous animal and human studies have documented an anti-tumor effect of allogeneic bone marrow transplantation (BMT) which is due not only to ablation of the leukemia by chemotherapy and radiation but also to a direct graft versus leukemia (GVL) activity provided by the graft itself [1-3]. Leukemia relapse rates are higher in syngeneic compared with allogeneic BMT, and recipients of T-cell-depleted grafts have a higher relapse rate than those receiving non-T-cell depleted grafts [4-7]. The GVL effect correlates with the development of graft versus host disease (GVHD).

Based on this GVL effect, numerous patients who have relapsed following allo-BMT have been treated with donor lymphocyte infusions (DLI) which are mononuclear cells obtained by apheresis from the original bone marrow or stem cell donor. Durable complete remissions have been noted in 50-70% of patients with chronic myelogenous leukemia (CML) [8-16]. Some responses, albeit less impressive, have been noted in patients with acute hematologic malignancies [12, 16-17]. Although the GVL response with DLI also correlates with the development of acute GVHD, the morbidity and mortality associated with Grades III-IV GVHD are significant. A mechanism for preserving the GVL response while controlling GVHD could greatly enhance the utility of DLI not only in acute and chronic leukemias, but in solid tumors as well.

Gene therapy strategies employing conditionally lethal 'suicide' genes and pro-drugs have engendered increasing interest in recent years. Several enzyme-pro -drug systems have been explored but most studies have used the *Herpes Simplex* virus enzyme thymidine kinase (HSV-TK) and ganciclovir (GCV) [18-24].

Exposure of mononuclear cells expressing HSV-TK virus thymidine kinase (HSV-TK) gene to GCV results in cellular apoptosis. GCV is a nucleoside analogue that is monophosphorylated by HSV-TK and further phosphorylated by mammalian cellular kinases to GCV-triphosphate which inhibits DNA polymerase and initiates chain termination of DNA synthesis. The TK gene is expressed in cells but is phenotypically silent in the absence of ganciclovir. The TK gene acts as a suicide agent in the presence of ganciclovir, since the monophosphorylated and higher phosphorylated forms of ganciclovir kill the cells in which the TK gene is expressed [22].

Infusion of donor lymphocytes transduced with HSV-TK in patients undergoing relapse following allogeneic bone marrow transplant (BMT) could provide a control mechanism for the immune response. The appropriate timing of GCV administration could lead to optimization of the anti-tumor effect followed by ablation of the cells to control chronic GVHD. The purpose of the proposed clinical strategy is to determine the safety and potential efficacy of HSV-TK transduced mononuclear cell infusions in patients who have relapsed or have persistent disease after allogeneic stem cell transplant. The goal is to define a minimum cell dose of HSV-TK transduced mononuclear cells which maintains a graft-versus-tumor effect, but induces minimal GVHD. Treatment with ganciclovir leading to destruction of the transduced lymphocytes will allow control of the GVHD produced without the need for immunosuppressive therapy. Induction of the graft-versus-tumor effect may not, however, be separable from the GVHD, thereby requiring multiple mononuclear cell infusions.

The clinical strategy is to use this process to prepare HSV-TK transduced donor leukocytes (TK-DLI) for infusion into patients whose hematologic malignancy persists or has relapsed following allogeneic BMT, followed by treatment with ganciclovir if GVHD occurs.

References

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