Scientific Abstract

A Phase 1 Dose Escalation Study Evaluating Safety and Feasibility of BPX-501 T Cells after Haploidentical αβTCR Cell-Depleted HSCT

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Allogeneic blood or marrow transplantation (alloBMT) is a potentially curative therapy for a variety of hematologic malignancies, including acute and chronic leukemia, myelodysplasia, lymphoma, and multiple myeloma. Approximately 50% of subjects who could benefit from alloBMT have neither an HLA-identical sibling, nor an HLA-identical unrelated donor. One potentially attractive alternative source of stem cells is a partially HLA-mismatched or HLA-haploidentical relative. In this context of immune genetic disparity between patient and donor, although mature donor T cells present in the graft facilitate T-cell reconstitution, they are responsible for the occurrence of graft-versus-host disease (GvHD), a severe, sometimes fatal, immune complication, which also impairs patient's immune reconstitution.

Strategies to prevent GvHD after HLA-haploidentical allo-HSCT based on either pharmacological immunosupression or T-cell depletion of the graft have been developed. A milestone in the history of haplo-HSCT was the demonstration that an efficient T-cell depletion of the graft is able to prevent both acute and chronic graft-versus-host disease (GvHD) even when using a related donor differing at the three major HLA loci (Reisner 1983). The benefits of T-cell depleted haploHSCT were first demonstrated in children with severe combined immunodeficiency (SCID). Clinical trials performed using of T-cell depletion based on the positive selection of CD34 cells from peripheral blood have confirmed that sustained engraftment of donor hematopoiesis, without the occurrence of GvHD, can be obtained in the majority of adult patients and that a substantial proportion of them, especially those affected by acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS), became long-term survivors. The feasibility and efficacy of haplo-HSCT was reproduced also in children with acute leukemia, as documented in few pilot studies enrolling a limited number of patients. While this approach improved rates of engraftment, overall a higher treatment related morbidity and mortality was noted in adults receiving a T-cell depleted grafts using the CD34+ selected stem cells due to delayed immunologic reconstitution (Ciurea 2010; 2012). This new trial attempts to compensate for this significant limitation by using a new Miltenyi device which partially depletes the haploidentical graft.

Most studies have used a myeloablative total body irradiation (TBI) based preparative regimen for haploidentical transplantation. However, there is a high rate of regimen-related toxicity and treatment-related mortality with this approach, particularly in adults. Reduced-intensity conditioning regimens have been developed to decrease regimen-related mortality and allow treatment of older patients or patients with concurrent medical conditions. Ciurea and colleagues studied the feasibility of the Fludarabine, melphalan and thiotepa (FMT) reduced-intensity preparative regimen in adult patients with advanced hematologic malignancies receiving a T cell depleted haploidentical graft. Also a retrospective analysis performed at MDACC revealed an improved day-100 treatment-related mortality, NRM and OS for patients treated with FMT compared with the prior experience with myeloablative, TBI-based preparative regimens. Ciurea

and others have noted a very low incidence of GVHD (less than 10%) with the T-cell depleted approach, but graft rejection, immune reconstitution and lack of T-cell mediated graft-vs-malignancy effects remain challenges.

Since immune reconstitution remains a challenge with any form of T cell depletion, especially in the first 180 days post-transplant, the addition of mature T cells early post-transplant which exhibit a broad repertoire of T cell immunity against viral antigens, as well as cancer antigens, might provide a significant clinical benefit. However, an expected side effect of the presence of T cells is the potential occurrence of aGvHD. The use of a suicide gene switch which would trigger the initiation of the apoptosis (killing) of the alloreactive T cells by the infusion of dimerizer drug (AP1903) would represent the potential means for restoring early immunity with a built in "safety switch" against GVHD side effects.

Our strategy is to combine haplo-identical, partially T cell depleted HSCT with addback of BPX-501 T cells, carrying a suicide gene, immediately after the HSCT is completed. We propose to utilize the iCasp9 suicide system (CaspaCIDe) consisting of a pro-apoptotic molecule, human caspase 9, joined to a drug-binding domain derived from human FK506-binding protein; which upon addition of a small molecule synthetic drug (AP1903) leads to homodimerization of caspase 9. Activation of the caspase pathway leads to rapid induction of apoptosis and death of the cells. Should severe GvHD develop after the infusion of the iCasp9 suicide T cells, the T cells will be destroyed upon administration of AP1903. The dimerizer drug, AP1903, has demonstrated a favorable safety profile in humans. To ensure that the majority of infused T cells carry the suicide gene, a selectable marker, truncated human CD19 (ΔCD19) was incorporated into the retroviral vector to enable enrichment for transduced cells using a commercial selection device prior to infusion into the patient.

The goal of this study is to determine whether the BPX-501 infusion after partially mismatched, related (haploidentical), αβ T cell-depleted HSCT can enhance immune reconstitution and potentially improve the graft versus leukemia (GVL) effect, with the potential for reducing the severity and duration of severe acute GvHD. The trial will evaluate the treatment of GvHD by the infusion of dimerizer drug (AP1903) in those subjects who present with non-skin acute GvHD (Grades II- IV) as well as those subjects with Grade I and II skin who progress on corticosteroid therapy or do not respond within 3 days.