Clinical outcome after adoptive infusion of BPX-501 cells (donor T cells transduced with iC9 suicide gene) in children given α/β T-cell depleted HLA-haploidentical hematopoietic stem cell transplantation (haplo-HSCT): preliminary results of a phase I-II trial.


Background

We recently completed a prospective study of more than 100 patients (ClinicalTrial.gov identifier: NCT01810120) which showed that haplo-HSCT after depletion of α/β T cells is an effective option for those children in need of an allograft and lacking an immediately available HLA-identical related or unrelated donor. This represents the “historical controls” for the BPX-004 study. However, recovery of adaptive T-cell immunity remains suboptimal and some patients died due to viral infections in the early post-transplant period. Thus, strategies aimed at accelerating early recovery of adaptive T-cell immunity are desirable.

Technology

All children received >10x10^6 CD34+ cells/kg and >1x10^7 α/β T cells/kg in the allograft. BPX-501 donor derived T cells are manufactured under GMP, expanded, transduced with the iCasp9 suicide gene and then cryopreserved and shipped back to the clinical site.

Study Design

We designed a phase I/II trial aimed at testing the safety and efficacy of post-transplant infusion of donor-derived T cells transduced with the iC9 suicide gene (BPX-501) in children with malignant or non-malignant disorders (ClinicalTrials.gov identifier: NCT02065869); enrollment started in December 2014. Cells are administered within 14 ± 4 days after haplo-HSCT. The phase I portion of the trial consisted of a classical 3+3 design with 3 cohorts, receiving escalating doses of BPX-501 cells of 2.5 x 10^5, 5 x 10^5, and 1x10^6/kg, respectively. Patients included in the phase II portion received the highest dose identified during the phase I portion of the study for a maximum of 60 children in both phase I/II portions of the study. All children with acute leukemia were transplanted in morphological complete remission (CR). Demographics, age and gender of patients enrolled in BPX-004 did not differ from historical control patients.

Hematopoietic Engraftment

Time to engraftment was evaluated in all patients with >40 days follow up, and was not statistically different from the historical patients being primarily dependent on the CD34 content of the allograft.

Immune Reconstitution

• In non-malignant patients who received BPX-501, a mean improvement was detected of approximately 40 days in achieving a T cell count of 500 cells/ul when compared to historical controls.
• When all patients were analyzed, a mean improvement was detected of approximately 25 days in achieving a T cell count of 500 cells/ul when compared to historical controls.
• Immune reconstitution with 500 CD3+ T cells historically correlates with improved clinical outcomes.
• All patients who have been discharged after transplant are evaluable for analysis which is ongoing.

100 Day Chimerism

• In 4 patients, mixed chimerism was present at the time of BPX-501 cell infusion and completely reverted to full donor chimerism subsequently.
• 1 SCD patient remains healthy with 20% partial chimerism.

Diagnosis of BPX-004 Enrolled Patients

<table>
<thead>
<tr>
<th>Diagnosis of Patients in BPX-004</th>
<th>N=49</th>
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</thead>
<tbody>
<tr>
<td><strong>Diagnosis Type: Malignant (N=21)</strong></td>
<td></td>
</tr>
<tr>
<td>Acute Lymphoblastic Leukemia</td>
<td>15</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
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</tr>
<tr>
<td>Burkitt Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Juvenile Myelomonocytic Leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>1</td>
</tr>
</tbody>
</table>

• Data from the BPX-004 cohort represents all patients treated with BPX 501 who have >40 days follow up.
• 4 with skin Gr 1 only; 1 patients with skin Gr II, and 2 patients with skin and gut Gr II— all resolving with SOTC.
• There has been no chronic GVHD seen in the 23 patients with >120 days follow up.

Incidence of GVHD vs Historical Controls

- There is no TRM in all BPX-004 patients who have received BPX-501 with at least 30 days follow up in the study to date (n=37).
- In particular, there is no TRM in the non-malignant group, which appears significantly different from historical controls.
- Although most BPX-004 patients have less than 1 year follow up, since TRM often occurs early in the post-transplant period in non-malignant patients, most often due to infectious complications, these data represent very exciting preliminary findings.

Time to Discharge and Re-hospitalization in Nonmalignant Patients

- In non-malignant patients who received BPX-501, there appeared to be a significant difference in median days to discharge after HSCT, and in the number of rehospitalizations after discharge.
- All patients who have been discharged after transplant are evaluable for analysis which is ongoing.

Transplant Related Mortality in NonmalignantPts

- There is no TRM in all BPX-004 patients who have received BPX-501 with at least 30 days follow up in the study to date (n=37).
- In particular, there is no TRM in the non-malignant group, which appears significantly different from historical controls.
- Although most BPX-004 patients have less than 1 year follow up, since TRM often occurs early in the post-transplant period in non-malignant patients, most often due to infectious complications, these data represent very exciting preliminary findings.

Summary

1. These data indicate that the infusion of BPX-501 cells is safe and well tolerated, with an improved TRM compared to historical controls receiving α/β T cell depletion.
2. The cumulative incidence of grade II-IV acute GvHD observed in these patients is similar if not better compared to historical controls.
3. BPX-501 cells expand in vivo and persist over time, accelerating the recovery of adaptive T-cell immunity, with improved clinical outcomes such as reduced duration of viral infections, reduced hospitalizations for infections.
4. Phase 2 dose of BPX-501 was determined to be 1 million/kg, but increased doses will be evaluated going forward for the malignant patients.
5. The iC9 cell-suicide system may increase the implementation of cellular therapy approaches aimed at optimizing immune recovery after transplantation.


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