Inducible-caspase-9 transduced T cells (BPX-501) after haplo-HSCT in children

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Haploidentical Donors: Evolution of T-cell Depletion Strategy

1995

1. CD34+ Selection “pure stem cells”

2010

2. TCRαβ/CD19 Depletion stem cells + effectors (NK cells + γδ-T cells)
Inducible-caspase-9 transduced T cells after haplo-HSCT in children

Generation of alloreactive NK cells and their therapeutic role in haplo-HSCT

A Novel Strategy for HSC Transplantation from Haploidentical Donors: Depletion of α/β T Cells

Inducible-caspase-9 transduced T cells after haplo-HSCT in children

Locatelli F et al, Front Immunol 2013
Inducible-caspase-9 transduced T cells after haplo-HSCT in children

Historical Cumulative Incidence of TRM
(patients transplanted from Nov 2010 – Sept 2014)

- Sibling
- MUD
- Haplo

p=0.15

N=51, E=6, TRM 11.8% (95% CI 4.7-22.3)
N=80, E=4, TRM 5% (95% CI 1.6-11.4)
N=41, E=1, TRM 2.4% (95% CI 0.2-11.2)

Number at risk
- 41 31 19 8 1
- 51 35 24 13 5
- 80 56 34 20 7

Years
0 1 2 3 4
Inducible-caspase-9 transduced T cells after haplo-HSCT in children

Historical Cumulative Incidence of Relapse (patients transplanted from Nov 2010 – Sept 2014)

Cumulative incidence

Years

Number at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>Sibling</th>
<th>MUD</th>
<th>Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>31</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>51</td>
<td>35</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>80</td>
<td>56</td>
<td>34</td>
<td>20</td>
</tr>
</tbody>
</table>

p=0.72

N=41, E=11, RI 32.2% (95% CI 16.6-48.9)

N=51, E=10, RI 22.2% (95% CI 11.1-35.7)

N=80, E=17, RI 21.9% (95% CI 13.4-31.8)
Inducible-caspase-9 transduced T cells after haplo-HSCT in children
Inducible-caspase-9 transduced T cells after haplo-HSCT in children

Historical Viral Reactivations / Infections (patients transplanted from Nov 2010 – Sept 2014)

- N=51, E=37, CI 72.5% (SE 16.5)
- N=80, E=47, CI 59.5% (SE 8.1)
- N=41, E=20, CI 48.7% (SE 7.4)

Cumulative incidence

Months

Number at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Sibling</th>
<th>MUD</th>
<th>Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>41</td>
<td>51</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td>20</td>
<td>16</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>30</td>
<td>12</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>40</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>50</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

p=0.005
Inducible-caspase-9 transduced T cells after haplo-HSCT in children
CD34+ cells → HPCs → Thymus → Recent thymic emigrants/naïve T cells

- GvHD
- TBI
- Sex steroid hormones
- Corticosteroids
- Aging
- KGF
- IL-7, IL-22
- LHRH-analogues
- Type-3 ILC

DLIs
Infusion of non-alloreactive T cells
T cells transduced with suicide genes
Pathogen-specific T cells
Treg/Tcon infusion

BPX–501: Inducible Caspase 9 T cells

“iC9 “Suicide Gene”

“Inducible” Binding site for Rimiducid – starts caspase apoptosis cascade

Truncated CD19 marker allows selection for purity and tracking in blood

- From normal donor leukapheresis -- GMP facilities US / Europe
- Activated and expanded in culture, transduced with the iC9 suicide gene and selected for CD19+ cells
- Cryopreserved and stored in liquid nitrogen
- Maintain characteristics of normal T cells
  - Broad T cell repertoire
  - Antiviral and antigen specific activity
BP-004 Study
Phase I/II Study of BPX-501 T Cells from an HLA-partially Matched Family Donor After Negative Selection of TCR αβ+ T Cells in Pediatric Patients With Hematological (malignant and non-malignant) Disorders

ClinicalTrials.gov identifier: NCT02065869
EUDRACT number: 2014-000584-41

Sponsor: Bellicum Pharmaceuticals
(first patient treated Dec 2014)

Participating Centers in Europe:
Ospedale Pediatrico Bambino Gesù
Great Ormond Street Hospital
Great North Children's Hospital Research Unit
University of Freiburg Clinic

Participating Centers in US:
Baylor College of Medicine Center for Cell and Gene Therapy, Feigin Center
Children's Hospital Los Angeles; Children's Healthcare of Atlanta at Egleston
Boston Children's Dana Farber; Children's National Medical Center
Seattle Children’s Hospital/UW/FHRCC; Children's Hospital – OHSU
Children’s Hospital UT SW; The Children's Hospital at Montefiore
Inducible-caspase-9 transduced T cells after haplo-HSCT in children
## BP-004 Study design

### Phase I portion:

**Classical 3+3 design**

2.5 X 10^5, 5 X 10^5 and 1 X 10^6 BPX-501 T Cells/kg

### Phase II portion:

**MTD/RD**

1 X 10^6 BPX-501 T Cells/kg

- Haploidentical donor (usually a parent)
- Non-mobilized apheresis for BPX-501 product
- TCRαβ/CD19-Depleted Allograft
- BPX-501 T cells Infused Day 14 + 4 post Tx
- No Post-Transplant GVHD Prophylaxis
- Rimiducid (AP1903) Used for Uncontrollable GVHD
Characterization of BPX-501: T Cell Phenotype Compared to Apheresis

After expansion and transduction, BPX-501 T cells have increased effector phenotype in both CD4 and CD8 T cell populations.
Characterization of BPX-501: Viability pre and post-thaw

- 49 infused BPX-501 T cell products (both malignant and non-malignant patients)
- High viability post cryopreservation and thaw
Treatment of GVHD with Rimiducid in US BP-004 Patient

- 15 month old non-malignant patient received $5 \times 10^5$ BPX-501 T cells/kg
- Progressive skin acute GVHD after topical steroids – patient received rimiducid
Variables considered in the choice of the haplo donor:

- NK alloreactivity according to the KIR/KIR ligand model
- KIR genotype B/x better than A/A
- Higher B content score (in particular CenB)
- Presence of licensed KIR2DS1 when C2⁺ patient
- Donor/recipient HCMV serology
- Larger size of alloreactive subset
- Donor age
- Donor gender (mother better than father)
Stem cell graft characterization

Nucleated Cells
1.15x10^9/Kg (range 0.6-1.9)

**IDEAL GRAFT COMPOSITION**

- High CD34+
- High γδ
- High NK
- Low αβ
- Low CD20+

**CD34+**
- 20.0x10^6/Kg (range 12.1-28.2)

**γδ**
- 15.2x10^6/Kg (range 3.88-38.9)

**NK**
- 33.5x10^6/Kg (range 23.9-97.5)

**αβ**
- 3.6x10^4/Kg (range 0.4-9.4)

**CD20+**
- 2.5x10^4/Kg (range 0.3-20)
<table>
<thead>
<tr>
<th>Patients characteristics (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Gender:</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>Median age at diagnosis (years):</td>
</tr>
<tr>
<td>Median age at HCST (years):</td>
</tr>
<tr>
<td>Median Follow-up (months):</td>
</tr>
</tbody>
</table>
## Patients characteristics (2)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>17 (100%)</th>
</tr>
</thead>
</table>

### Disease:

<table>
<thead>
<tr>
<th>ALL</th>
<th>13 (76%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph+</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>t(4;11)</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AML</th>
<th>4 (24%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0/M7</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>7-/complex caryotype</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>secondary AML</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CR at HSCT</th>
<th>17 (100%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CR1/CR2</th>
<th>7/10 (41/59%)</th>
</tr>
</thead>
</table>
## Donor characteristics (1)

<table>
<thead>
<tr>
<th>Donors</th>
<th>17 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years):</td>
<td>35 (26 – 48)</td>
</tr>
</tbody>
</table>

**Donor:**

<table>
<thead>
<tr>
<th>Mother</th>
<th>9 (53%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>8 (47%)</td>
</tr>
</tbody>
</table>

**Sex mismatch**

<table>
<thead>
<tr>
<th>Female-&gt;Male</th>
<th>6 (35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-&gt;Male</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Donors</td>
<td>17 (100%)</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>NK alloreactivity</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>11 (65%)</td>
</tr>
<tr>
<td>NO</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>B/X</td>
<td>15 (88%)</td>
</tr>
</tbody>
</table>
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Cumulative incidence of ANC and PLT recovery for the malignant cohort

Median 11 days (range 9-13)

Median 17 days (range 10-22)
## Acute & chronic GvHD in Malignant Cohort

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD I-II Skin Only</td>
<td>3</td>
<td>topical steroids</td>
<td>resolved</td>
</tr>
<tr>
<td>Acute GVHD III Visceral</td>
<td>2</td>
<td>Systemic steroids</td>
<td>resolved</td>
</tr>
<tr>
<td>Acute GVHD IV Visceral</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Mild Chronic GVHD</td>
<td>2</td>
<td>Systemic steroids</td>
<td>resolved</td>
</tr>
<tr>
<td>Severe Chronic GVHD</td>
<td>1</td>
<td>Systemic steroids Rimiducid infusion</td>
<td>improved (bil. decreased)</td>
</tr>
</tbody>
</table>
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Probability of DFS for the whole cohort of patients

1-yr DFS 92.9% (SE 6.8)

Median follow.up: 7 months
Inducible-caspase-9 transduced T cells after haplo-HSCT in children
Inducible-caspase-9 transduced T cells after haplo-HSCT in children
Impact of CMV reactivation on BPX-501 expansion on BP-004 patients

Inducible-caspase-9 transduced T cells after haplo-HSCT in children
Expansion of iC9-transduced T Cells in BP-004 Patient

CD3+/CD19+ and CMV reactivation

![Graph showing CD3+/CD19+ and CMV reactivation over days post HSCT]

- CD3+/CD19+ (\(\mu l\))
- CMV DNA (copies/ml)

![Bar graph showing IFN-\(\gamma\) SFC/10^5 PBMC response to various stimuli]

- Media
- PHA
- EBV
- pp65
- IE1
- IE2

CMV proteins
BPX-501 T cells in Bone Marrow

CD3+CD19+ in Bone Marrow

Time from HSCT (days)

cells/ml

0 100 200 300 400

0 200 400 600
<table>
<thead>
<tr>
<th></th>
<th>CU#1</th>
<th>CU#2</th>
<th>CU#3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>14 years</td>
<td>18 months</td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>Refractory AML</td>
<td>Refractory AML</td>
<td>1° relapse refractory AML</td>
</tr>
<tr>
<td><strong>Type of donor</strong></td>
<td>father</td>
<td>mother</td>
<td>mother</td>
</tr>
<tr>
<td><strong>Conditioning regimen</strong></td>
<td>TBI+TT+L-PAM (after CLOVE)</td>
<td>BU+Cy+L-PAM (after CLOVE)</td>
<td>Treo+TT+L-PAM (after CLO-ARAc)</td>
</tr>
<tr>
<td><strong>Engraftment</strong></td>
<td>Yes (day +18)</td>
<td>Yes (day +11)</td>
<td>Yes (day +13)</td>
</tr>
<tr>
<td><strong>Acute and chronic GvHD</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>No</td>
<td>Yes (4 mos)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Last follow-up</strong></td>
<td>Alive &amp; well (+ 13 mos)</td>
<td>Dead due to disease recurrence</td>
<td>Alive &amp; well (+ 4 mos)</td>
</tr>
</tbody>
</table>
1. BPX-501 cells once infused expand *in vivo* and persist over time, contributing to recovery of adaptive immunity

2. No patient has died of infections, GvHD or other transplant-related complications

3. Although the follow-up is still limited, the relapse rate in these children with acute leukemias given BPX-501 cells compares favorably with that of the historical controls

4. No patient developed PTLD

5. This approach renders haplo-HSCT an attractive option for children with acute leukemia in need of an allograft

6. Future studies will address the role of repeated infusions or higher numbers of BPX-501 cells in patients with fully resistant disease
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