Administration of Rimiducid Following Haploidentical Rivo-cel T Cells in Children With Malignant or Non-Malignant Disorders Who Develop Graft-versus-Host-Disease

Abstract #2207

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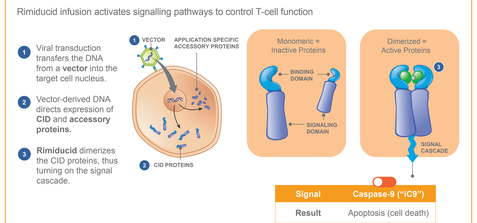
BACKGROUND

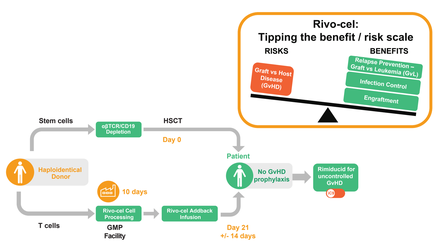
- Allogeneic hematopoietic stem cell transplantation (HSCT) constitutes a curative treatment for children with many different malignant and non-malignant disorders[1]
- HLA–partially matched haploidentical (haplo) donors represent a suitable alternative option for those children who lack an HLA-compatible donor[1,2]
- T-cell depletion approaches with positive selection (CD34+) or negative selection (αβ T-cell and CD19+ B-cell depletion) may allow engraftment of donor cells with a low risk of graft-versus-host disease (GvHD)[1,2]
  - However, success is limited by delayed immune recovery, thus increasing the risk of fatal infections
  - Add-back of unmanipulated donor T cells to accelerate immune recovery is associated with a high risk of GvHD
- Rivogenlecleucel (rivo-cel, BPX-501) is an allogeneic product consisting of T cells modified to express the inducible caspase-9 (iC9) safety switch (**Figure 1**)
  - The polyclonal nature of rivo-cel provides broad virus- and tumor-specific immunity
  - The iC9 safety switch, induced by dimerization through administration of rimiducid, has the unique ability to promptly and durably resolve symptoms of GvHD

Figure 1. Chemical Induction of Dimerization (CID) Molecular Switch Platform



- **Figure 2** depicts rivo-cel T cells, which are:
  - Derived from unmobilized donor leukapheresis
  - Produced in Good Manufacturing Practice facilities in Europe and the United States
  - Activated and expanded in culture
  - Transduced with the iC9 suicide gene and selected using the CD19+ marker
  - Cryopreserved and stored in liquid nitrogen
- Normal T-cell characteristics are maintained, including:
  - Broad T-cell repertoire
  - Antiviral and antitumor immunity

Figure 2. Rivo-cel Addresses the "T-Cell Dilemma" in Haplo-HSCT



GMP, Good Manufacturing Practice; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; iC9, inducible caspase-9; TCR, T-cell receptor.

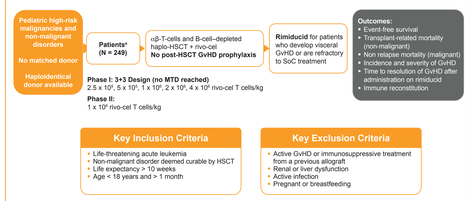
OBJECTIVES

- To evaluate the safety and efficacy of rimiducid in the treatment of GvHD following administration of rivo-cel T cells in pediatric patients with malignant or non-malignant disorders given αβ T-cell and B-cell–depleted haplo-HSCT
  - A key objective of this study is to assess the activity of rimiducid infusion following onset of visceral GvHD or GvHD that is refractory to standard-of-care treatment

METHODS

- In 2 multicenter prospective trials (US [NCT03301168] and EU [NCT02065869]), αβ T-cell and B-cell–depleted haplo-HSCT was followed by infusion of a titrated number of donor lymphocytes genetically modified with the iC9 safety switch (rivo-cel T cells) in patients with malignant or non-malignant disorders (**Figure 3**)
- Patients who developed visceral GvHD or were refractory to standard-of-care treatment were eligible to receive ≥ 1 dose of rimiducid
  - Rimiducid 0.4 mg/kg was administered over 2 hours

Figure 3. Study Design



[a] ATG was administered from Day-4 to Day -2 (12-15 mg/kg over 3 consecutive days) and rituximab at a dosage of 200 mg/m^2 on Day -1.

ATG, anti-thymocyte globulin (rabbit); GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MTD, maximum tolerated dose; SoC, standard of care.

- GvHD response:
  - Complete response (CR) was defined as resolution of all manifestations in each organ or site
  - Partial response (PR) was defined as improvement in ≥ 1 organ or site without progression in any other organ or site
- Patients received one of several different myeloablative conditioning regimens depending on their underlying disease and age and whether they had undergone previous autologous HSCT
- Per protocol, rivo-cel T cell infusion was scheduled on day 21 ± 14 following the allograft
- No post-transplantation pharmacological GvHD prophylaxis was used
- Patients who developed visceral GvHD or were refractory to standard-of-care treatment were eligible to receive ≥ 1 dose of rimiducid
  - Per protocol, GvHD treatment guidelines recommended use of corticosteroid (topical or systemic) per institutional guidelines
  - If progression or lack of adequate response occurred, patients could receive a single dose of rimiducid
  - The protocol was later amended to allow for up to 3 doses of rimiducid (at 48-hour intervals) based on investigator discretion

Statistical Analysis

- Study participants who received HSCT and rimiducid and had ≥ 1 follow-up assessment were included in the efficacy-evaluable population (EEP)
- Clinical cutoff: September 17, 2018

RESULTS

Patient Characteristics

- As of the clinical cutoff:
  - 249 patients received HSCT
  - 229 patients received HSCT and rivo-cel
- Key baseline patient characteristics (patients receiving HSCT) are shown in **Table 1**
  - The median age at HSCT was 6.6 years; malignant or non-malignant disease was reported in 47% and 53% of patients, respectively

Table 1. Key Baseline Characteristics

Characteristic	N = 249
Male / female, n (%)	135 (54.2) / 114 (45.8)
Median age at HSCT, years	6.6 (0.2 – 22.1)
Median HSCT dose, CD34+ 10^6/kg	18.0 (3 – 57)
Median time to rivo-cel infusion, days	18.0 (7 – 147)
Disease diagnosis, n (%)	
Malignant	117 (47)
ALL	54 (21.7)
AML	47 (18.9)
Other[a]	16 (6.4)
Non-Malignant	132 (53)
Thalassemia major	25 (10)
SCID	24 (9.6)
Fanconi anemia	14 (5.6)
Other[b]	69 (27.7)
Conditioning regimen, n (%)[c]	
TBI-based	97 (39)
Busulfan-based	89 (35.7)
Treosulfan-based	42 (16.9)
Cyclophosphamide-based	6 (2.4)
Fludarabine-based	4 (1.6)
Other	7 (2.8)
Donor, n (%)	
Parent	229 (92)
Sibling	17 (6.8)
Half-sibling	3 (1.2)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; SCID, severe combined immunodeficiency; TBI, total body irradiation.

[a] Other malignant disorders include Hodgkin lymphoma, juvenile myelomonocytic leukemia, myelodysplastic syndrome, and non-Hodgkin lymphoma.

[b] Other non-malignant disorders include autoimmune hemolytic anemia, bone marrow aplasia, CD40 ligand deficiency, chronic granulomatous disease, combined immunodeficiency disease, complement deficiency, complex autoimmune disease without molecular diagnosis, Diamond-Blackfan anemia, dock 8 deficiency, Epstein-Barr virus–induced T-gamma lymphoproliferative disease, hemophagocytic lymphohistiocytosis, hyper-IgD syndrome-mevalonate kinase deficiency, IKBα gain of function mutation, IL-2 receptor deficiency, IL-10 RB deficiency, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, MHC class II deficiency, osteopetrosis, paroxysmal nocturnal hemoglobinuria and bone marrow failure, Shwachman-Diamond syndrome, sickle cell disease, Wiskott-Aldrich syndrome, and X-linked inhibitor of apoptosis deficiency.

[c] Four patients did not have conditioning regimen entered in the clinical database at time of clinical cutoff.

GvHD

- Of the 249 patients who received HSCT, 238 were evaluable for GvHD occurrence
  - 54 patients (22.7%) developed acute GvHD, all grades, before 100 days
    - 29 cases were grade II-IV
    - 7 cases were grade III-IV
  - 21 additional cases of late-onset GvHD (after 100 days) were reported
    - 13 cases were grade II-IV
    - 6 cases were grade III-IV
  - 10 patients (5.6%) developed mild to severe chronic GvHD
    - 8 cases were moderate to severe chronic GvHD

Clinical Response

- As of clinical cutoff, 24 patients met the rimiducid EEP definition
- The concomitant medications to treat GvHD administered prior to rimiducid were representative of GvHD standard treatment regimens
- The median duration of GvHD treatment prior to first rimiducid administration was 68 days (range, 14-309 days)
- The best overall clinical response (CR/PR) within 7 days after rimiducid administration was 70% (16 responders) (**Table 2**)
  - A CR or PR to rimiducid was observed in 9 and 7 patients, respectively
- Median time to initial response (per protocol evaluated within 7 days after rimiducid administration) was 1 day (range, 1-4 days)

Table 2. Clinical Response by Subject Within 7 Days Post Rimiducid Administration

Subject	GvHD Type	Overall GvHD Grade	Organ Stage	Response
Patient 1	Acute	Grade I	Stage 2 skin	PR
Patient 2	Acute	Grade I	Stage 2 skin	PR
Patient 3	Acute	Grade I	Stage 2 skin	CR
Patient 4	Acute	Grade II	Stage 3 skin	PR
Patient 5	Acute	Grade II	Stage 3 skin	CR
Patient 6	Acute	Grade II	Stage 3 skin	CR
Patient 7	Acute	Grade II	Stage 3 skin	PR
Patient 8	Acute	Grade II	Stage 3 skin	PR
Patient 9	Acute	Grade II	Stage 3 skin	CR
Patient 10	Acute	Grade II	Stage 3 skin, stage 1 gut	PR
Patient 11	Acute	Grade II	Stage 3 skin	CR
Patient 12	Acute	Grade II	Stage 2 skin	NR
Patient 13	Acute	Grade II	Stage 1 UGI	NE[a]
Patient 14	Acute	Grade II	Stage 1 skin, stage 1 UGI	CR
Patient 15	Acute	Grade II	Stage 3 skin	CR
Patient 16	Acute	Grade II	Stage 3 skin	CR
Patient 17	Acute	Grade III	Stage 3 liver	PR
Patient 18	Acute	Grade III	Stage 2 gut, stage 1 UGI	NR
Patient 19	Acute	Grade III	Stage 3 skin, stage 3 gut	NR
Patient 20	Acute	Grade III	Stage 3 liver	NR
Patient 21	Acute	Grade III	Stage 3 gut, stage 1 UGI	CR
Patient 22	Acute	Grade III	Stage 2 gut	NR
Patient 23	Chronic	Moderate	Score 2 lungs, score 1 eyes	PR
Patient 24	Chronic	Severe	Score 3 liver, score 2 lung	NR

CR, complete response; NE, non-evaluable; NR, non-response; PR, partial response; UGI, upper gastrointestinal.

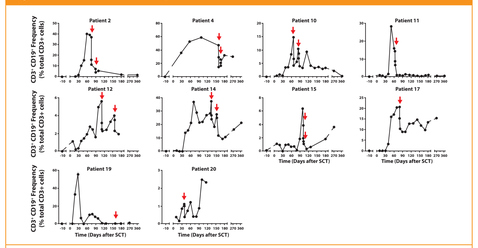
[a] Response data was not included in the clinical database at time of clinical cut off.

- Four patients who achieved a PR or non-evaluable response within the first 7 days following rimiducid administration went on to achieve CR within 30 days following rimiducid administration
- Median number of doses received was 1 (range, 1-2)
- Nine patients (42.9%) received a second dose of rimiducid
  - Most patients had PR or no response at the time of the second dose of rimiducid
  - 2 patients in PR at the time of the second dose of rimiducid went on to achieve CR
- Of the 24 patients in the rimiducid EEP, 14 had malignant disease
  - 11 patients with malignant disease remain relapse free

Immunological Assessment

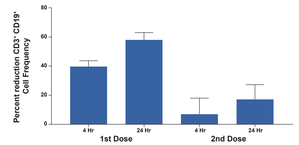
- At the time of clinical cutoff, 10 patient samples were available for immunologic assessment
- All patients who received rimiducid for treatment of GvHD and from whom samples were received for analysis showed an initial reduction in rivo-cel T cells following administration of drug (**Figure 4a**)
- The frequency of rivo-cel T cells within the total T-cell population was reduced an average of 33.9% ± 6.3% and 59% ± 3.8% at 4 and 24 hours, respectively, after the first dose of rimiducid (**Figure 4b**)
- Four of six patients who received a second dose of rimiducid showed an average reduction of 34.6% ± 9.8% in rivo-cel T-cell frequency within 24 hours of the second rimiducid infusion (**Figure 4a, 4b**)

Figure 4A. Cell Death in Response to Rimiducid[a]



[a] Red arrow indicates rimiducid administration. SCT, stem cell transplantation.

Figure 4B. Reduction in Rivo-cel Frequency in Peripheral Blood Following Rimiducid Infusion



CONCLUSIONS AND IMPLICATIONS

- These data suggest that administration of rimiducid for treatment of GvHD with visceral involvement or refractoriness to standard-of-care therapy represents a novel and highly effective treatment approach in pediatric patients with non-malignant or malignant disorders who received αβ T-cell and B-cell depleted haplo-HSCT followed by infusion of rivo-cel T cells
- The administration of rimiducid in children given rivo-cel T cells allows for effective control of GvHD occurring after the adoptive transfer of genetically modified T cells
- Data presented by Zhou et al (abstract 3496) demonstrate that rimiducid-dependent killing of rivo-cel T cells requires sufficient transgene expression, which is regulated by the activation state of the cell
  - Rimiducid effectively eliminates the most highly activated rivo-cel T cells, which express the highest level of iC9

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DISCLOSURES

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- Franco Locatelli: Advisory board, Bellicum Pharmaceuticals
- Melissa Aldinger: Bellicum Pharmaceuticals
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