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Posoleucel, an Allogeneic, Off-the-Shelf Multi-Virus Specific T Cell Therapy, for Severe, Drug-Refractory Viral Infections in Pediatric Patients Following HCT

Results from a Phase 2 Trial

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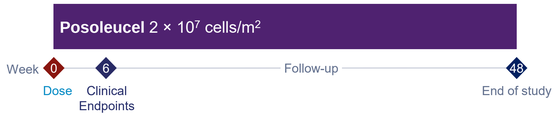
BACKGROUND

- Recipients of allogeneic hematopoietic cell transplantation (allo-HCT) are susceptible to infections from and reactivation of double-stranded DNA viruses, which are a major cause of morbidity and mortality
- The small number of published studies focusing on pediatric allo-HCT recipients indicate that the course of viral diseases and their treatment are generally similar in pediatric and adult patients, but some differences in the populations have been noted:
  - Children are less likely to have had prior CMV infection than adults, and are thus at higher risk for acquiring CMV from their donor[1]
  - Children appear to be more susceptible to AdV infections than adults[2]
- Conventional antiviral drugs are used to prevent and treat these infections in the pediatric population, but their efficacy is modest and often accompanied by severe toxicities
- Because of the lack of dedicated pediatric studies, practice recommendations have been extrapolated from studies in adult patients

Posoleucel

- Posoleucel is an off-the-shelf multi-virus-specific T-cell (VST) therapy that targets 6 viruses common in immunocompromised patients: adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus-6 (HHV-6), and JC virus (JCV)
- The phase 2 CHARMS study (NCT02108522), which was conducted at Baylor College of Medicine from June 2014 to Nov 2019, evaluated the feasibility and safety of posoleucel in allo-HCT recipients with ≥1 of these viruses who were either unresponsive to or unable to tolerate standard antiviral therapies
- Of the 58 allo-HCT recipients treated in CHARMS, 55 (95%) had a complete or partial response[3]
- The population of CHARMS included 18 patients under the age of 18 years
- We analyzed the safety and antiviral activity of posoleucel in these patients

CHARMS Study Design



- Phase 2, proof-of-concept, open-label study designed to assess the safety and antiviral activity of posoleucel in allo-HCT recipients of any age with ≥1 treatment-refractory infections
- Patients received a single infusion of 2 × 10^7 cells/m^2 posoleucel with the option to receive a second infusion after 4 weeks and additional infusions at biweekly intervals thereafter
- Key eligibility criteria: infection with AdV, BKV, CMV, EBV, HHV-6, and/or JCV
  - Failure of antiviral therapy OR
  - Unable to tolerate standard antivirals
- Safety: Acute grade 3 to 4 graft-vs-host disease (GVHD) within 42 days of the last dose of posoleucel, and grade 3 to 5 non-hematologic adverse events related to posoleucel within 28 days of the last infusion
- Efficacy: Antiviral response was assessed 6 weeks after the first dose
  - Complete response (CR): return of viral load to normal range as well as resolution of clinical signs and symptoms
  - Partial response (PR): viral load reduction of ≥50% or a 50% improvement of clinical signs and symptoms

RESULTS

Baseline Demographics

Patient Characteristics	N=18
Age, median years (range)	10 (2, 16)
Male, n (%)	10 (56)
Viral infections at baseline, n (%)*	
AdV	6 (33)
BKV	10 (56)
CMV	4 (22)
EBV	0
HHV-6	3† (17)
JCV	1 (6)
Number of viral infections, n (%)	
1	13 (72)
2 concurrent	3 (17)
2 sequential	1 (6)
3 concurrent	1 (6)

*Viral infections at baseline represents individual viruses and not patients.
†One of these patients was later confirmed to have chromosomal genomic integration of HHV-6.

Safety and Tolerability

Events	N=26
Patients with any treatment-emergent AE	18 (100)
Patients with treatment-related AEs	11 (61)
Common treatment-related AEs	
Pyrexia	4 (22)
Lymphocyte count decreased	2 (11)
Neutrophil count decreased	2 (11)
White blood cell count decreased	2 (11)
Maculopapular rash	2 (11)
Treatment-related SAEs	4 (22)*
Any treatment-related grade ≥3 TEAE, n (%)	5 (28)
AE leading to dose reduction, interruption, or d/c	0
Cytokine release syndrome	0
Deaths (neither was related to study treatment)	2 (11)

*Four patients experienced 7 treatment-related SAEs: pyrexia, pneumonia, atelectasis, pulmonary edema, acute GVHD (GI), adenovirus infection, neurological decompensation.

Acute GVHD within 42 Days of Last Dose

Age (yrs)	Sex	History of aGVHD	aGVHD at Baseline	Affected Organ	Maximum GVHD Grade during Study
4	F	Y	N	Skin	1
9	M	Y	Y	Skin	1
12	M	Y	N	Skin	1
12	F	N	N	Skin	1
15	F	Y	Y (diff. dx: infection)	GI tract	3

One patient (6%) had acute GVHD grade ≥2
The incidence of acute GVHD among the pediatric patients in CHARMS (5/18, 28% [95% CI, 10, 53]) did not differ meaningfully from the incidence among adults (8/40, 20% [95% CI, 9, 36])

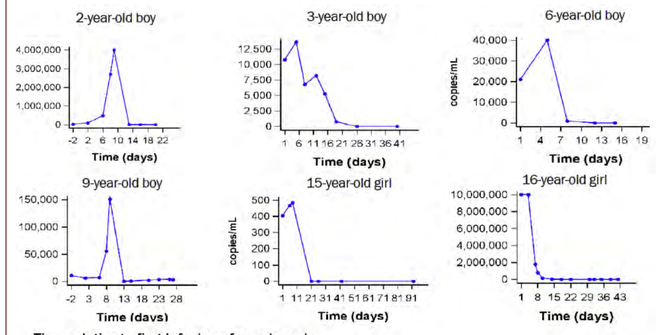
Outcomes by Patient and Virus

Age (yrs)	Sex	Initial diagnosis	No. of PSL infusions	# of shared HLA alleles	Target virus at study entry	Outcome
2	M	AML	2	3	AdV BKV	PR PR
3	F	Hurler Syndrome	1	1	CMV	PR
3	M	Beta Thalassemia	1	2	AdV	PR
4	F	Hodgkin Lymphoma	2	3	CMV	PR
5	M	MDS	1	3	BKV	PR
6	M	Chronic Granulomatous Disease	1	4	AdV BKV CMV	CR PR PR
9	M	Severe AA and Secondary Monosomy	1	2	BKV	PR
9	M	ETV6-RUNX1 - ALL	2	4/3†	AdV BKV	CR PR
10	F	ALL	2	4	HHV-6*	PR
10	F	ALL	2	2	BKV HHV-6	PR PR
12	M	ALL	3	3/4†	BKV	PR
12	F	Glanzmann Thrombasthenia	1	4	BKV	PR
12	M	Chronic Granulomatous Disease	1	3	BKV	PR
14	M	ALL	2	2	HHV-6	PR
15	F	SCID	1	4	AdV	CR
15	M	Severe Congenital Neutropenia	1	4	CMV	PR
16	F	AA	1	1	BKV	PR
16	F	ALL	2	2	ADV JCV	CR PR

Eighteen of 18 patients (100%) achieved a clinical response (CR or PR) by 6 weeks including all 5 patients infected with multiple target viruses.

*This patient was subsequently discovered to have genomic integration of HHV-6.
†These patients received a different line of posoleucel on second infusion.
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; SCID, severe combined immunodeficiency; AA, aplastic anemia.
PR, partial response; CR complete response.

Viral Loads (Blood) in Patients with Adenovirus Infection



CONCLUSIONS

- Posoleucel was well tolerated by this pediatric population
- No patient experienced cytokine release syndrome
- Posoleucel appeared to demonstrate efficacy in pediatric patients with refractory viral infections
- All pediatric patients receiving posoleucel had a clinical response
- Phase 3 studies including pediatric patients are in progress:
  - Multi-virus prevention in allo-HCT recipients (NCT05305040)
  - Treatment of virus-associated hemorrhagic cystitis in allo-HCT recipients (NCT04390113)
  - Treatment of AdV infection in allo-HCT recipients (NCT05179057)

References

1. Otto WR, Green A. Antiviral therapeutics in pediatric transplant recipients. Infect Dis Clin N Am. 2022;36:125-46.
2. Howard DS, Phillips II GL, Reece DE, et al. Adenovirus infections in hematopoietic stem cell transplant recipients.Clin Infect Dis. 1999;29;1494-501.
3. Pfeiffer T, Tzannou I, Wu M, et al. Posoleucel, an allogeneic, off-the-shelf multi-virus specific T cell therapy, for the treatment of refractory viral infections in the post-HCT setting. Clin Cancer Res 2022 (in press).

Disclosures

BO, pending patent applications in the field of engineered T-cell therapies for cancer. AML, co-founder of AlloVir and Marker Therapeutics, consultant CSO of AlloVir. IPF, BP, DW, employees of and hold stock in Allovir. HEH has equity in Allovir and Marker Therapeutics, has served on advisory boards for Tessa Therapeutics, Novartis, Gilead, GSK, Kiadis and Fresh Wind Biotechnologies and received research support from Tessa Therapeutics and Kuur Therapeutics..

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