Poster ALL-173

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Evolution of tisagenlecleucel use for the treatment of pediatric and young adult relapsed/refractory B-cell acute lymphoblastic leukemia: Center for International Blood & Marrow Transplant Research (CIBMTR) registry results

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KEY FINDINGS AND CONCLUSIONS

- Pediatric and young adult patients with R/R B-ALL are receiving tisagenlecleucel earlier in their treatment course
- Incorporation of tisagenlecleucel into the treatment landscape of R/R B-ALL has reduced the use of HSCT, including in high-risk and vulnerable patient subgroups (e.g., patients aged <3 years)
- OS and RFS curves were not substantially affected by post-infusion HSCT
  - Use of next generation sequencing in detecting minimal residual disease, where available, can be considered to assess risk of relapse and/or need for subsequent therapies, including HSCT (as opposed to B-cell recovery)
- Safety outcomes were favorable overall, likely due to treatment of patients with lower disease burden and more real-world experience in management of CRS and neurotoxicity
- Studies exploring consolidative HSCT in patients who achieve remission after tisagenlecleucel should attempt to identify those at highest risk of relapse, and assess whether HSCT in these patients could improve outcomes

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INTRODUCTION

- Tisagenlecleucel is an autologous CD19-directed chimeric antigen receptor T-cell immunotherapy indicated for patients up to 25 years of age with B-cell acute lymphoblastic leukemia (B-ALL) that is refractory in second or later relapse[1]
- As patient selection has evolved over time, real-world and retrospective studies have continued to demonstrate efficacy and safety of tisagenlecleucel in patients with relapsed and/or refractory (R/R) B-ALL[2,3]
- Hematopoietic stem cell transplant (HSCT) has been considered the standard of care for pediatric patients with very high-risk ALL in first or second complete remission[4-5]
  - Avoidance of HSCT, especially in patients at high risk of transplant-related toxicities (infertility, endocrine dysfunction, cognitive and developmental issues, growth effects, graft versus host disease, and secondary malignancies),[6-9] may improve outcomes

OBJECTIVE

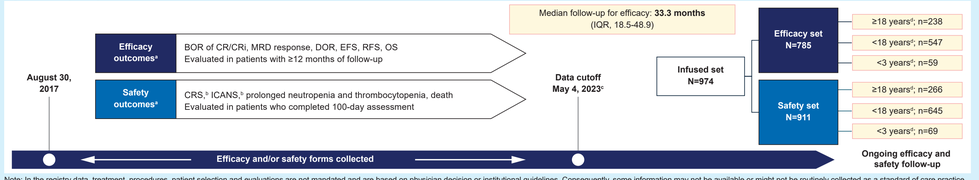
- Examine the impact of tisagenlecleucel on the patient treatment journey since the Food and Drug Administration approval in 2017

METHODS

Study Design

- Data were collected as a part of a noninterventional, prospective, longitudinal study using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry (**Figure 1**)
- Patients were treated in the United States, Canada, Korea, or Taiwan

Figure 1. Study design



Note: In the registry data, treatment, procedures, patient selection and evaluations are not mandated and are based on physician decision or institutional guidelines. Consequently, some information may not be available or might not be routinely collected as a standard of care practice
[a]Center-reported. [b]ASTCT grading criteria. [c]Patients who died or discontinued prior to data cutoff were also included. [d]At time of infusion.
ASTCT, American Society for Transplantation and Cellular Therapy; BOR, best overall response; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete remission; CRi, CR with incomplete hematologic recovery; CRS, cytokine release syndrome; DOR, duration of response; EFS, event-free survival; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival.

RESULTS

Baseline Disease Characteristics by Age Group

- As of May 4, 2023, 974 patients received tisagenlecleucel
- Patients <3 years had an increased frequency of lysine methyltransferase 2A (*KMT2A*) rearrangement, central nervous system (CNS) involvement, first relapse/primary refractory disease than patients ≥18 years (**Table 1**)
- Patients ≥18 years had an increased frequency of Philadelphia chromosome-positive ALL, high disease burden (≥50% bone marrow [BM] blasts), third or greater relapse, prior cell therapy, prior allogeneic HSCT, and prior exposure to blinatumomab and inotuzumab than patients <3 years (**Table 1**)
- Patients ≥18 years had more prior exposure to blinatumomab and inotuzumab than patients <18 years (**Table 1**)

Table 1. Baseline disease characteristics by age group

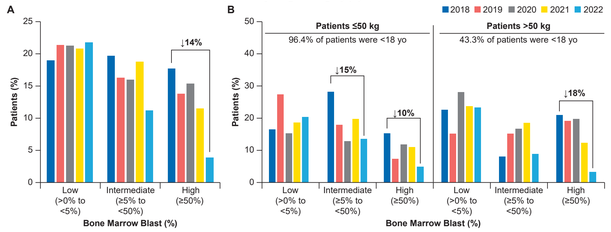
Subgroups by Baseline Characteristics, n (%)	≥18 Years n=287	<18 Years n=687	<3 Years n=75
Abnormal *KMT2A* rearrangement	27 (9.4)	107 (15.6)	54 (**72.0**)
Ph+ ALL	22 (**7.7**)	36 (5.2)	0
>0% to <5% BM blasts	62 (21.6)	141 (20.5)	13 (17.3)
≥5% to <50% BM blasts	36 (12.5)	119 (17.3)	13 (17.3)
≥50% BM blasts	44 (**15.3**)	71 (10.3)	8 (10.7)
Morphologic CR	103 (35.9)	294 (42.8)	31 (41.3)
MRD⁻	63 (22.0)	153 (22.3)	15 (20.0)
MRD⁺	33 (11.5)	112 (16.3)	13 (17.3)
Primary refractory	31 (10.8)	72 (10.5)	9 (**12.0**)
1st relapse	66 (23.0)	177 (25.8)	28 (**37.3**)
≥3rd relapse	30 (**10.5**)	32 (4.7)	2 (2.7)
Down syndrome	9 (3.1)	46 (6.7)	0
CNS involvement	26 (9.1)	57 (8.3)	14 (**18.7**)
Prior cell therapy	18 (**6.3**)	25 (3.6)	0
Prior allogeneic HSCT	75 (**26.1**)	145 (21.1)	12 (16.0)
Prior blinatumomab	77 (**26.8**)	109 (15.9)	13 (17.3)
Prior inotuzumab	50 (**17.4**)	49 (7.1)	7 (9.3)

One patient ≥18 years received a prior autogenic HCT; one patient ≥18 years received a prior autogenic and allogenic HCT.
KMT2A previously referred to as 11q23/MLL rearrangement.
ALL, acute lymphoblastic leukemia; BM, bone marrow; CNS, central nervous system; CR, complete remission; HCT, hematopoietic cell transplantation; HSCT, hematopoietic stem cell transplant; KMT2A, lysine methyltransferase 2A; MLL, mixed lineage leukemia; MRD, minimal residual disease; Ph+, Philadelphia chromosome positive.

Disease Burden

- High disease burden (≥50% BM blasts) at the time of infusion decreased from 18% in 2018 to 4% in 2022 (**Figure 2A**)
- High disease burden at the time of infusion has decreased over time by 10% and 18% in patients ≤50 kg and >50 kg, respectively (**Figure 2B**)
- Intermediate disease burden (≥5% to <50% BM blasts) at the time of infusion has decreased over time by 15% in patients ≤50 kg (**Figure 2B**)

Figure 2. Disease burden at the time of infusion (A) and by weight category (B) over time

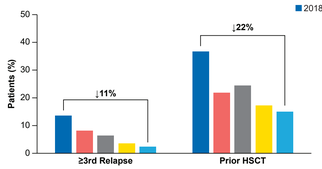


Low disease burden: >0% to <5% bone marrow blasts; intermediate disease burden: ≥5% to <50% bone marrow blasts; and high disease burden: ≥50% bone marrow blasts. (A) Low, intermediate, and high disease burden at the time of infusion in 2017 (August 30-December 31) was 16.7%, 8.3% and 8.3%, respectively. Low, intermediate, and high disease burden in 2023 up to May 4, 2023, was 18.2%, 12.1% and 6.1%, respectively. (B) Proportion of patients <18 years reported from the efficacy evaluable set. Patients with missing weight were not included. Low, intermediate, and high disease burden at the time of infusion in 2017 (August 30-December 31) in patients ≤50 kg was not captured; low, intermediate, and high disease burden in 2023 up to May 4, 2023, in patients ≤50 kg was 25.0%, 12.5% and 12.5%, respectively. Low, intermediate, and high disease burden at the time of infusion in 2017 (August 30-December 31) in patients >50 kg was 28.6%, 14.3% and 14.3%, respectively. Low, intermediate, and high disease burden in 2023 up to May 4, 2023, in patients >50 kg was 0%, 9.1% and 0%, respectively.
yo, years old.

Patients Are Receiving Tisagenlecleucel Earlier in the Course of Their Treatment

- The number of patients in ≥3rd relapse and those who received prior HSCT decreased over time (**Figure 3**)

Figure 3. Proportion of patients receiving tisagenlecleucel in the course of their treatment over time

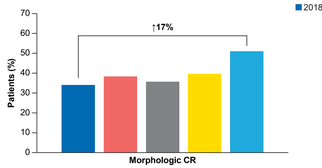


The proportion of patients in ≥3rd relapse at the time of infusion in 2017 (August 30-December 31) was 0%; the proportion of patients in ≥3 relapse at the time of infusion in 2023 up to May 4, 2023, was 6.1%. The proportion of patients who had received a prior HSCT in 2017 (August 30-December 31) was 33.3%; the proportion of who had received a prior HSCT in 2023 up to May 4, 2023, was 6.1%.
HSCT, hematopoietic stem cell transplant.

Increase in Patients in Morphological Complete Remission at the Time of Infusion Over Time

- A higher proportion of patients received tisagenlecleucel while in morphological complete remission in 2022 (51%) than in 2018 (34%) (**Figure 4**)

Figure 4. Proportion of patients with morphological complete remission at the time of infusion

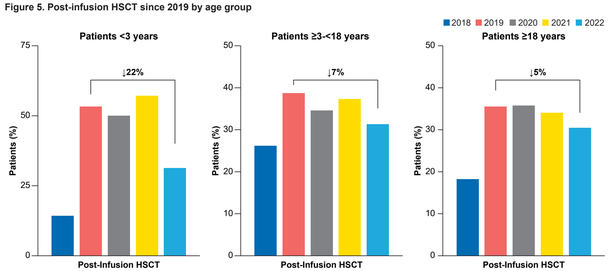


The proportion of patients in morphological CR at the time of infusion in 2017 (August 30-December 31) was 58.3%; the proportion of patients in morphological CR in 2023 up to May 4, 2023, was 51.5%.
CR, complete remission.

Decrease in Post-Infusion HSCT Since 2019

- Overall, 34.5% (314/911) of patients received post-infusion HSCT (**Figure 5**)
- Reasons for post-infusion HSCT were not captured for most patients

Figure 5. Post-infusion HSCT since 2019 by age group

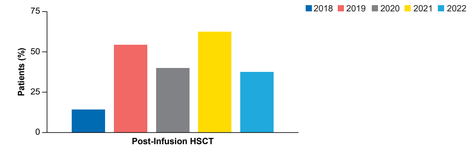


Bar charts present data from the Infused Set.
Post-infusion HSCT frequency in 2017 (August 30-December 31) in patients <3 years was 0%; post-infusion HSCT frequency in 2023 up to May 4, 2023, in patients <3 years was 0%. Post-infusion HSCT frequency in 2017 (August 30-December 31) in patients 3-18 years was 16.7%; post-infusion HSCT frequency in 2023 up to May 4, 2023, in patients 3-18 years was 0%. Post-infusion HSCT frequency in 2017 (August 30-December 31) in patients >18 years was 40.0%; post-infusion frequency in 2023 up to May 4, 2023, in patients 3-18 years was 0%.
HSCT, hematopoietic stem cell transplant.

Post-infusion HSCT Frequency in Patients <3 Years With *KMT2A* Rearrangements

- 72.0% (54/75) of pediatric patients aged <3 years had a *KMT2A* rearrangement
  - 43.4% (23/53) of patients with *KMT2A* rearrangement underwent post-infusion HSCT (**Figure 6**)
  - Reasons for post-infusion HSCT were not captured for most patients

Figure 6. Post-infusion HSCT frequency in patients <3 years with *KMT2A* rearrangements

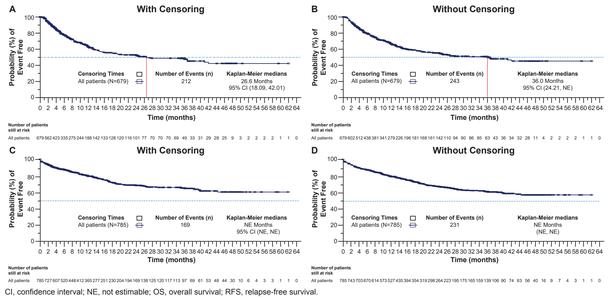


KMT2A rearrangement frequency in patients <18 and ≥18 years was 15.6% and 9.4%, respectively. The overall rate of post-infusion HSCT in patients <3 years with *KMT2A* rearrangements in 2017 (August 30-December 31) was 25.0%. The overall rate of post-infusion HSCT in patients <3 years with *KMT2A* rearrangements in 2023 up to May 4, 2023, was 0%.
HSCT, hematopoietic stem cell transplant; *KMT2A*, lysine methyltransferase 2A.

Relapse-Free Survival (RFS) and Overall Survival (OS) With and Without Censoring of Post-Infusion HSCT

- The 36-month OS probabilities with and without censoring were 66% (95% CI, 61-71) and 62% (95% CI, 57-66), respectively (**Figure 7**)

Figure 7. RFS (A-B) and OS (C-D) with and without censoring of post-infusion HSCT



CI, confidence interval; NE, not estimable; OS, overall survival; RFS, relapse-free survival.

Long-Term Safety of Tisagenlecleucel

- Long-term safety profile remains favorable across age groups and consistent with previous reports (**Table 2**)

Table 2. Safety of tisagenlecleucel across age groups

Adverse Events, n (%)	≥18 Years n=266	<18 Years n=645	<3 Years n=69
Cytokine release syndrome (within 100 days)	163 (61.3)	368 (57.1)	44 (63.8)
Grade ≥3	43 (16.2)	99 (15.3)	5 (7.2)
Neurological events (within 100 days)	58 (21.8)	135 (20.9)	10 (14.5)
Grade ≥3	23 (8.6)	60 (9.3)	7 (10.1)
Subsequent neoplasms	4 (1.5)	7 (1.1)	3 (4.3)
Prolonged neutropenia	66 (24.8)	126 (19.5)	13 (18.8)
Prolonged thrombocytopenia	70 (26.3)	108 (16.7)	12 (17.4)
Clinically significant infections	177 (66.5)	362 (56.1)	49 (71.0)
Bacterial	79 (29.7)	141 (21.9)	19 (27.5)
Fungal	23 (8.6)	25 (3.9)	2 (2.9)
Parasitic	1 (0.4)	1 (0.2)	0 (0)
Viral	96 (36.1)	204 (31.6)	19 (27.5)
Unspecified	33 (12.4)	57 (8.8)	10 (14.5)

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