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ORAL ABSTRACTS

612.ACUTE LYMPHOBLASTIC LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Toxicity Profile of Brexucabtagene Autoleucel (brexu-cel; CD19-directed CAR T-cell therapy) in Adult Patients (pts) with Relapsed/Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (B-ALL): Results from a Multicenter Real-World Outcomes Study

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Introduction:
In October 2021, the FDA approved brexu-cel for the treatment of adults ≥ 18 years old with R/R B-ALL. Following this approval, a consortium of cancer centers was formed across the US to investigate outcomes following commercial brexu-cel use for adults with R/R B-ALL. One area of interest is the toxicity profile of brexu-cel when given in the real-world context, including the respective incidences and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS).
Methods:
Eligible pts included adults ≥ 18 years old who received commercial brexu-cel starting in October 2021 onward at a participating center in the US (N = 25). Retrospective patient data were collected across participating institutions, with the most recent data lock occurring on June 30, 2023. Criteria from the ASTCT were used to grade CRS and ICANS severity. Statistical methods included the use of medians and simple ratios for descriptive outcomes; univariate logistic regression models were used to assess the association of various factors with the probability of CRS and ICANS, and Cox regression was used to examine the association of each with the hazards of mortality and failure for event-free survival (EFS; earliest of progression, relapse, or death).
Results:
Key demographics and toxicities are described in Tables 1 and 2 (respectively). Of the 152 pts infused with brexu-cel, 82% (N = 125) developed CRS and 56% (N = 85) developed ICANS. CRS and ICANS did NOT develop in 12% (N = 19). Twenty percent of all pts (N = 31) required ICU-level care for management of CAR-related toxicities, with a median LOS in ICU of 4 days (range 1-79). In univariate models, grade 3+ ICANS was most likely to occur in pts with active disease (≥ 5% marrow blasts and/or EMD) at the time of apheresis (OR 2.63, 1.28-5.38, p = 0.008); a numerical increase for grade 3+ CRS (OR 2.35, 0.69-8, p = 0.17) was seen in pts with active disease at apheresis.
Therapies received for these CAR-related toxicities included steroids, tocilizumab (toci), and anakinra (Table 2). Among pts who received steroids (N = 94), 37% (N = 34) achieved a sufficient response to the first steroid trial and did not require subsequent therapies; otherwise, toxicities improved with the first steroid course but later worsened in 16% (N = 15); the first trial of steroids was not effective but improved when further steroids were given in 31% (N = 29); there were no responses to any doses of steroids in 10% (N = 9). In pts receiving toci (N = 103), 31% (N = 32) achieved a sufficient response to the first dose and did not require any further therapy; toxicities improved with the first dose but later worsened in 31% (N = 32); the first dose was ineffective but improvement was seen with subsequent doses in 21% (N = 22); 9% (N = 9) did not respond at all to toci.
The rate of death within day +28 was 6% (N = 9), and the respective causes were typically multifactorial: CRS was implicated in 3 cases, ICANS in 3, infection in 5, disease relapse/progression in 2, and HLH in 1 case. In total, uncontrolled ICANS was implicated in the death of 6 pts (between day +9 to day +106). HLH was reported in 6 pts: in most cases, this was a biochemical diagnosis, and it either overlapped with concurrent CRS or infection or occurred following CRS/ICANS. The most common infections between day 0 and day +28 included bacteremia in 8% of pts (N = 12), fungal infections in 4% (N = 6), pneumonia in 3% (N = 5), and CMV infections in 3% (N = 4). The fungal infections included 4 instances of invasive sinopulmonary infections (2 due to aspergillus; 2 due to mucormycosis) and 2 cases of candidemia.
With both CRS and ICANS treated as a time-varying covariate, the development of grade 3+ CRS was associated with a higher hazard of death (HR 2.38, 1.00-5.66, p = 0.05); grade 3+ ICANS was not associated with a demonstrably higher risk of death (HR 1.11, 0.60-2.05, p = 0.74). The HR of EFS failure for Grade 3+ CRS was 1.81 (0.87-3.79, p = 0.12) and for grade 3+ ICANS HR = 0.93 (0.56-1.53, p = 0.77).
Conclusions:
In this real-world study of toxicities from brexu-cel use for adults with R/R B-ALL, we observed CRS and ICANS in the majority of pts, and no new safety signals were observed. Rates of severe CRS and ICANS were more common with active disease. Interestingly, though CRS-related mortality was rare, grade 3+ CRS was associated with a higher risk of death. Efforts to identify mechanisms and mitigable risk factors for these toxicities are warranted.

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Table 1: Baseline characteristics of adults treated with brexu-cel for R/R B-ALL

Factor	# (%) or Median (Range)
Demographic/clinical	
Age, median, range	46 (18-81)
Sex, male	87 (57%)
Race/ethnicity: non-Hispanic white	77 (51%)
Race/ethnicity: Hispanic/Latino	52 (34%)
Ph-	102 (67%)
Ph+	47 (31%)
Prior lines of therapy	4(1-12)
Disease burden at apheresis*	
>5% blasts	78 (51%)
CR MRD+	35 (23%)
CR MRD-	23 (15%)
CR MRD status unknown	3 (2%)

* This measurement was used for all analyses of associations between disease burden and toxicity as it was more universally available in this cohort.

Table 2: Details on toxicities associated with brexu-cel for adults with R/R B-ALL

Factor	# (%) or Median (Range)
CRS	
All grades	125 (82%)
Grade 1	58 (38%)
Grade 2	53 (35%)
Grade 3	9 (6%)
Grade 4	4 (3%)
Unknown	6 (4%)
ICANS	
All grades	85 (56%)
Grade 1	14 (9%)
Grade 2	21 (14%)
Grade 3	34 (22%)
Grade 4	14 (9%)
Unknown	1 (3%)
Total number developing CRS and/or ICANS	133 (88%)
CRS time-to-onset, days	5 (0-14)
CRS duration, days	4 (1-22)
ICANS time-to-onset, days	7 (0-21)
ICANS duration, days	4 (1-30)
Maximum ferritin, ng/mL	3683 (0.13-294117)
Maximum CRP, mg/L	35 (0.16-608)
Treatment for CAR-related toxicities	
Corticosteroids	94 (62%)
Steroid exposure in mg of dexamethasone equivalents	70 (1-2047)
Tocilizumab	103 (68%)
Total doses of tocilizumab	2 (1-5)
Anakinra	32 (21%)
Other	6 (4%)
Length-of-stay (LOS) in hospital, days	15 (0-95)
LOS in ICU for CAR-related toxicities, days	4 (1-79)

Figure 1

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