Abstract: PB3197

Title: LYMPHODEPLETION MATTERS FOR CAR T-CELLS IN AGGRESSIVE LARGE B-CELL LYMPHOMA

Abstract Type: Publication Only

Topic: Gene therapy, cellular immunotherapy and vaccination - Clinical

Background:

Lymphodepletion (LD) is an essential step in the procedure of chimeric antigen receptor T-cell (CAR-T) therapies as it maximizes engraftment, efficacy, and long-term survival of CAR-T. LD allows depletion and modulation of endogenous lymphocytes, conditioning of the microenvironment for improved CAR-T expansion and persistence, and reduction of tumor load. Combined Fludarabine (Flu) and cyclophosphamide (Cy) is the most commonly used LD in real-world practice for relapsed/refractory (R/R) aggressive large B-cell lymphomas (ALBCL) based on the pivotal clinical trials in second (2L) and third (3L) lines. However, Flu/Cy doses differed substantially: tisagenlecleucel (tisa-cel) Flu25/Cy250 x 3 days (d); axicabtagene (axi-cel) Flu30/Cy500 x 3d; lisocabtagene maraleucel (liso-cel) Flu30/Cy300 x 3d, with a similar wash out time of 2days.

Aims:

To evaluate the impact of a Flu30/Cy500 x 3d LD on the expansion of CAR T-cells, safety, and efficacy on patients (pts) with R/R ALBCL treated with tisa-cel in L3.

Methods:

Flu30/Cy500 x 3d was administered to 4 consecutive pts with R/R ALBCL treated in 3L with tisa-cel between July 2023 and Nov 2023. CAR T-cell expansion was monitored in blood by flow cytometry. The CAR-T expansion of the 4 pts was compared to that of 131 pts treated in our center with tisa-cel Flu25/Cy250 (control cohort, CC). Efficacy was assessed by CTscan, MRI for CNS involvement, and 18FDG-PET-CT based on the Lugano criteria. CTCAE version 4.0 was used to evaluate toxicities.

Results:

Pts presented R/R ALBCL (diffuse large B-cell lymphoma (DLBCL) n=2; transformed follicular lymphoma n=2) after 2 (n=3) or 3 (n=1) prior lines. Median age was 69.5 years (range 67;72), and 3 pts were (75%) males. Two pts presented a secondary central nervous system (CNS) infiltration. All pts received a bridging therapy. At the time of LD, 2 pts were in progressive disease. ECOG-PS was 1, except for one pt ECOG-PS=3. IPI was 1 for two pts, 2 for one, and 3 for one. Expansion was observed in all (100%) pts of the Flu30/Cy500 cohort, compared to 37/131 (28%) of the CC. The CAR T-cell expansion peak in blood was observed at day+7 in the Flu30/Cy500 cohort, compared to day+9 in the CC where expansion was observed (eCC, n=104). The median peak at 1368 CART/µL (range: 717 – 1606) in the Flu30/Cy500 cohort compared to 53 (range: 3-2900) in the eCC. The % of CART/T CD3+ lymphocytes was 15,75% (range 11.8 – 38.9) in the Flu30/Cy500 cohort compared to 7.4% (range: 1.2% - 75.5%) in the eCC. The AUC was 335 (range: 95 – 731) in the Flu30/Cy500 cohort.

In the Flu30/Cy500 cohort, CRS was grade 1 in two pts, grade 2 in one, grade 3 in one. CRS was treated with Tocilizumab (n=1), Siltuximab (n=1), and dexamethasone (n=2). ICANS was observed in 3 pts, of grades 1, 2, and 3, respectively. One pt received Anakinra. Hematotoxicity included grade 4 neutropenia (n=4), grade 3-4, thrombocytopenia (n=3), and grade 3 anemia (n=1). At M3, all (100%) pts of the Flu30/Cy500 cohort showed a complete metabolic response (CRm) including the 2 pts with CNS infiltration.

Summary/Conclusion:

LD with Flu30/Cy500 in pts treated with 3L tisa-cel showed an impact on quantitative and qualitative aspects of CAR-T expansion. Observed adverse events were expected and manageable. All patients showed a CRm at the time of analysis. These findings are encouraging for considering LD as a key parameter in CART and for working

on adapted personalized LD.

Expansion	FLU30/Cy500 n=4	eCC n=104
Onset, median	Day +7	Day+ 9
CART-cells/CD3,% (range)	15.7% (11.8 – 38.9)	7.4% (1.2 - 75.5)
CAR T-cells/mm^3, n (range)	1368 (717 -1606)	53 (3-2900)

Keywords: B cell lymphoma, CAR-T