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705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Permissive Cardiotoxicity As a Guiding Principle to CAR-T Therapy with Reduced Ejection Fraction Heart Failure

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Introduction: Pivotal CAR-T registrational trials for the six CAR-T therapies currently FDA approved have excluded those with heart failure (HF), defined either by low ejection fraction (EF) or clinical symptoms of HF (NYHA functional classification). This has created a real-world dilemma for clinicians desiring to treat this patient population. There is concern that those with HF may not tolerate the physiologic and hemodynamic stressors associated with cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) and thus have increased risk of severe morbidity or death. The emerging concept of permissive cardiotoxicity seeks to allow for an acceptable level of cardiac toxicity to allow for treatment with highly efficacious but potentially cardiac toxic treatments like CAR-T therapy. To that end, in this study, we provide our real-world, single-institution experience with CAR-T therapy in patients with medically optimized HF with reduced EF (HFrEF) prior to date of apheresis.
Methods: This was a retrospective review of 168 (100 B-cell lymphoma and 68 multiple myeloma) CAR-T therapy patients, with 20 (12%) identified with HFrEF of ≤50% prior to apheresis by two-dimensional transthoracic echocardiogram as part of the standard CAR-T screening process and without clinical symptoms of HF at time of apheresis. 19/20 patients received standard of care CAR-T products. This study was conducted following IRB approval. Statistical analysis was done using R version 4.2.3. Kaplan-Meier curves were used to calculate progression free survival(PFS) and overall survival(OS).
Results: Twenty patients with HFrEF prior to CAR-T infusion were identified with median EF of 44.1% (range 25-50%) (see Table 1, Baseline Characteristics). The median age was 63.5 (37-82) years-old, predominately male gender (80%), Caucasian (70%), with ECOG of 1 (95%), and 10 patients (50%) received axicabtagene ciloleucel (axi-cel). Most patients received CAR-T for B-cell lymphoma (80%). Cardiac history included 5 (25%) with previous CAD, 1 (5%) with previous PAD, and 4 (20%) with history of atrial fibrillation/flutter. Cardio-Oncology was consulted prior to CAR-T therapy in 10 (50%) and 12 (60%) were optimized on goal-directed therapy (GDT). CKD was pre-existing in 4 (20%) patients. Where measured, all patients had a pre-CAR-T troponin within normal institutional limits (<0.05ng/mL). NT-BNP at baseline was only measured in 6 (30%) patients with a median value of 110pg/mL (49-3200, upper limit of normal 125pg/mL). Longitudinal strain prior to CAR-T was measured in 5 (25%) patients with median value of -16% (-19 to -10%, <-17% normal).
There were no cases of grade ≥3 CRS with 3 (15%) grade 1 and 12 (60%) grade 2 CRS (see Table 1, Safety Outcomes). There were 4 (20%) with grade 3 ICANS, although most patients 12 (60%) did not experience ICANS. Compared to ZUMA-1, the 10

patients receiving axi-cel did not have significantly higher rates of CRS or ICANS. Tocilizumab was administered in 15 (75%) of patients and steroids given in 10 (50%) of patients. Following CAR-T infusion, 11 (55%) of patients required ICU admission, no patients required vasopressors, 6 (30%) experienced an AKI, 2 (10%) had LFT abnormalities, 4 (20%) had an arrhythmia, and 5 (25%) had further decline in EF with recovery occurring in most cases where measured. Only 2 (10%) of patients had an HF exacerbation within 30 days of CAR-T infusion. PFS and OS were 11.3 and 26 months, respectively.

Conclusion: Given that all registrational CAR-T trials excluded HF, notable reservation exists among clinicians in the use of CAR-T therapy in patients with a history of HF and particularly HFrEF. In our institutional experience of 20 patients with good performance status and medically optimized on GDT, we demonstrate that CAR-T therapy can be given safely with rates of CRS and ICANS similar to that expected in the non-HF population. Additionally, while ICU utilization was high, the incidence of arrhythmias, renal or hepatic toxicity as indicators of end organ dysfunction, non-recovering EF decline, and heart failure exacerbation following CAR-T infusion were quite low. It is thus our practice to consider CAR-T therapy on a case by case basis in those with a history of HFrEF. The key to success being maximal cardiac optimization achieved through early engagement of our Cardio-Oncology colleagues based upon the concept of permissive cardiotoxicity.

Disclosures Hoffmann: *BeiGene:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *Genentech:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *TG Therapeutics:* Consultancy, Honoraria; *Pharmacyclics:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *ADC Therapeutics:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Kite:* Consultancy, Honoraria. **McGuirk:** *Astellas Pharma:* Research Funding; *Fresenius Biotech:* Research Funding; *Novartis:* Research Funding; *EcoR1 Capital:* Consultancy; *Magenta Therapeutics:* Consultancy; *Allovir:* Consultancy, Research Funding; *Juno Therapeutics:* Consultancy; *Kite:* Consultancy, Research Funding; *Bellicum Pharmaceuticals:* Research Funding; *Gamida Cell:* Research Funding; *Pluristem Therapeutics:* Research Funding.

Table 1, Baseline Characteristics

Characteristic	Entire Cohort (n=20)	Axi-cel (n=10)
Age, in years		
Mean (SD)	62.1 (10.8)	62.0 (9.80)
Median [Min, Max]	63.5 [37.0, 82.0]	61.5 [45.0, 82.0]
Gender		
Female	4 (20.0%)	2 (20.0%)
Male	16 (80.0%)	8 (80.0%)
Race/Ethnicity		
African American	4 (20.0%)	1 (10.0%)
Asian American	2 (10.0%)	0 (0%)
Caucasian	14 (70.0%)	9 (90.0%)
ECOG		
1	19 (95%)	10 (100%)
2	1 (5%)	0
CAR-T Product		
Axicabtagene ciloleucel	10 (50.0%)	10 (100%)
Idecabtagene vicleucel	4 (20.0%)	0 (0%)
Tisagenlecleucel	5 (25.0%)	0 (0%)
TYB323	1 (5.0%)	0 (0%)
Costimulatory receptor		
4-1BB	10 (50.0%)	0 (0%)
CD28	10 (50.0%)	10 (100%)
History of Coronary Artery Disease		
Yes	5 (25.0%)	2 (20.0%)
Followed by Cardio-Oncology		
Yes	10 (50%)	3 (30%)
Goal directed therapy (GDT) for heart failure		
Yes	12 (60%)	5 (50%)
History of Peripheral Arterial Disease		
Yes	1 (5.0%)	0 (0%)
Troponin prior to CAR-T		
Mean (SD)	0.0233 (0.0158)	0.0300 (0.0283)
Median [Min, Max]	0.0200 [0.0100, 0.0500]	0.0300 [0.0100, 0.0500]
Not measured	11 (55.0%)	8 (80.0%)
nt BNP prior to CAR-T		
Mean (SD)	612 (1270)	NA (NA)
Median [Min, Max]	110 [49.0, 3200]	NA [NA,NA]
Not measured	14 (70.0%)	10 (100%)
LDH Prior to Lymphodepletion		
Mean (SD)	277 (131)	282 (167)
Median [Min, Max]	228 [158, 694]	194 [158, 694]
Ferritin prior to lymphodepletion		
Mean (SD)	488 (450)	390 (310)
Median [Min, Max]	320 [20.0, 1460]	314 [20.0, 1060]
Ferritin max to Day +30		
Mean (SD)	1570 (1910)	1460 (1670)
Median [Min, Max]	812 [138, 7500]	741 [413, 5630]
CRP prior to lymphodepletion		
Mean (SD)	1.28 (1.89)	0.829 (1.06)
Median [Min, Max]	0.770 [0.0200, 8.16]	0.275 [0.0300, 3.16]
Missing	1 (5.0%)	0 (0%)
CRP max to Day +30		
Mean (SD)	15.3 (8.75)	16.1 (7.47)
Median [Min, Max]	13.8 [4.21, 34.0]	14.5 [6.62, 26.3]
History of Chronic Kidney Disease		
Yes	4 (20.0%)	2 (20.0%)
EF prior to CAR-T		
Mean (SD)	44.1 (6.26)	45.6 (4.97)
Median [Min, Max]	45.0 [25.0, 50.0]	45.5 [35.0, 50.0]
Longitudinal Strain prior to CAR-T		
Mean (SD)	-14.4 (3.83)	-16.0 (0)
Median [Min, Max]	-16.0 [-19.0,-10.0]	-16.0 [-16.0, -16.0]
Not measured	15 (75.0%)	8 (80.0%)
History of atrial fibrillation/flutter		
Yes	4 (20.0%)	0 (0%)
Disease indication		
Myeloma	4 (20.0%)	0 (0%)
B-cell lymphoma	16 (80.0%)	10 (100%)

Table 1, Safety Outcomes

Safety Outcome	Entire Cohort (n=20)	Ax-cel (n=10)
Max CRS		
0	3 (15.0%)	1 (10.0%)
1	12 (60.0%)	5 (50.0%)
2	5 (25.0%)	4 (40.0%)
Max ICANS		
0	12 (60.0%)	3 (30.0%)
1	2 (10.0%)	2 (20.0%)
2	2 (10.0%)	2 (20.0%)
3	4 (20.0%)	3 (30.0%)
ICU Admission		
Yes	11 (55.0%)	7 (70.0%)
AKI to Day +15 (defined as Cr increase by 0.3 or > 1.5 times baseline)		
Yes	6 (30.0%)	3 (30.0%)
LFT abnormality >1.5 ULN AST/ALT or Tbili>1.5 to Day +30		
Yes	2 (10.0%)	2 (20.0%)
Arrythmia occuring from infusion to Day +30		
Yes	4 (20.0%)	4 (40.0%)
Use of Tocilizumab		
Yes	15 (75.0%)	8 (80.0%)
Use of Steroids		
Yes	10 (50.0%)	8 (80.0%)
Decline in EF (Y/N)		
Yes	5 (25.0%)	2 (20.0%)
Not measured	7 (35.0%)	3 (30.0%)
EF recovery w/in 12 months in those that had a post-CAR-T decline in EF		
No	1 (5.0%)	0 (0%)
Yes	5 (25.0%)	3 (30.0%)
Not measured	14 (70.0%)	7 (70.0%)
HF exacerbation within 30 Days of CAR-T		
Yes	2 (10.0%)	1 (10.0%)

Figure 1

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