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Subsequent Malignant Neoplasms in Patients Previously Treated with Anti-CD19 CAR T-Cell Therapy

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Abstract:

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Subsequent Malignant Neoplasms in Patients Previously Treated with Anti-CD19 CAR T-Cell Therapy

Running Title: Subsequent Malignant Neoplasms Post CAR T

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To The Editor:

Chimeric antigen receptor (CAR) T-cell therapy is a novel therapy that utilizes either gamma-retroviral or lentiviral vectors to genetically modify a patient's autologous T-cells to express an anti-CD19 antibody against CD19 positive B-cell malignancies [1,2]. Since 2017, three anti-CD19 CAR T-cell therapies, axicabtagene ciloleucel (axi-cel; Yescarta), tisagenlecleucel (tisa-cel; Kymriah), and lisocabtagene maraleucel (liso-cel; Breyanzi) have been FDA approved and have demonstrated remarkable efficacy in the treatment of relapsed and refractory B-cell non-Hodgkin lymphomas (NHLs) [3-8]. Initial long-term follow up of these pivotal clinical trials showed low rates of myelodysplastic syndrome (MDS) following CAR T-cell therapy and no other subsequent malignant neoplasms (SMNs) [9,10]. However, multiple real-world retrospective analyses examining outcomes following treatment with CAR T-cell therapy report varying rates of SMNs ranging from 0.9% to 12.9%, the most common of which being MDS [8-12]. These real-world studies are limited by small patient populations and often focus on the rate of treatment related myeloid neoplasms, with limited data regarding solid tumor or other hematologic malignancies. On November 28th, 2023, the FDA announced an investigation into reports of T-cell malignancies, including CAR-positive lymphomas, in patients who received treatment with BCMA- or CD19-directed autologous CAR T-cell immunotherapies [13,14]. These findings raise concern for an increased rate of secondary T-cell neoplasms related to potential insertional mutagenesis from genetically modified CAR T-cell therapy [15,16]. In light of the recent announcement by the FDA of reported cases of CAR-positive T-cell lymphomas following CAR T-cell therapy, we performed the largest retrospective analysis reported in the literature examining the rates of SMNs in patients previously treated with anti-CD19 CAR T-cell therapy, with particular attention to the incidence of T-cell neoplasms.

We identified 582 patients with relapsed and refractory LBCL treated with CAR T-cell therapy between 2015 and 2022 across 13 academic medical centers. Patients in this cohort received a median of 3 prior lines of therapy (range 1-18), including 224 patients previously treated with auto-HSCT and 6 patients who previously received an allogeneic-HSCT. Median follow-up in survivors was 35.3 months with a median progression free survival of 11.5 months (95% CI 6.08 – 16.92) and median overall survival of 27.8 months (95% CI 21.2 – 34.5). Seventeen patients had EBV positive disease, 4 had HIV infection, and 26 patients had a previously diagnosed autoimmune condition (Table 1).

Data on SMNs was captured in 549 patients. Forty-five (8.2%) of these patients developed a SMN following CAR T-cell therapy, at a median time of diagnosis of 19.3 months (range 4.0- 80.2) from the time of CAR T-cell infusions and 52.2 months (range 6.2- 279.4) from the time of initial diagnosis of B-cell lymphoma. The most common SMNs were myelodysplastic syndrome (18 patients), solid tumor (11 patients), acute myeloid leukemia (6 patients), and cutaneous malignancy (3 patients with squamous cell carcinoma and 2 patients with basal cell carcinoma) (Table 2). The patients who developed SMNs received a median of 3 prior lines of therapy (range 1-7), including 25 patients previously treated with auto-HSCT and 2 patients who previously received an allogeneic-HSCT. Additionally, 27 of these patients received bridging therapy prior to CAR T-cell infusion (regimen details outlined in table 2). No patients who developed a SMN were EBER or HIV positive and only 2 had pre-existing auto-immune conditions. Fourteen of the patients who developed a SMN (31.1%) had a history of prior tobacco use.

Of the 504 patients in our dataset who did not develop an SMN, 287 patients relapsed post CAR T-cell therapy at a median of 2.8 months (range 0.2- 57.3) and went on to receive a median of 1 subsequent line of therapy (range 1-7). Seventeen of the 45 patients who developed SMNs (38%) relapsed post CAR

T-cell therapy at a median of 7.7 months (range 0.79- 44.7) and went on to receive a median of 1 subsequent line of therapy (range 1-5). In 11 of these patients, SMN developed following relapsed disease and subsequent lines of therapy, 5 of which developed a myeloid neoplasm (1= AML, 4= MDS).

The median follow up of those patients who developed an SMN was 35 months at which time the median PFS following CAR T-cell therapy had not been reached. Twenty-nine of the 45 patients with SMNs were alive at last known follow up. Of the 16 deceased patients, 8 deaths were attributed to complications or progression of SMN with a median OS from time of diagnosis of SMN of 26 months.

One patient in our cohort developed a T-cell neoplasm: a 63-year-old man with a history of tobacco use, autoimmune colitis not on immunosuppressants, and Grey Zone Lymphoma (IPI of 4) was initially treated with dose adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide) with partial response (PR) to therapy. He was subsequently exposed to pembrolizumab with inadequate response and proceeded to CAR T-cell therapy with one dose of brentuximab-vedotin as bridge. He received axicabtagene ciloleucel and achieved a CR but was subsequently diagnosed with both a peripheral T-cell lymphoma, not otherwise specified (NOS) and a concurrent non-small cell lung cancer (NSCLC) approximately 4 months (121 days) after CAR-T cell infusion. The patient died of NSCLC 2 years after receiving CAR T-cell therapy. Unfortunately, genomic sequencing to evaluate involvement of the CAR-T cell in this T-cell neoplasm was not performed as tissue was not accessible.

Patients with a history of immune dysregulation, such as that associated with Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), autoimmune disease, or with the use of immunosuppressive agents, are at increased risk for developing both B- and T-cell lymphoproliferative neoplasms[17,18]. In fact, cases of concurrent B- and T-cell lymphomas have been widely documented in the literature occurring in 1-5% of cases of NHL with the most frequent being a combination of DLBCL and adult T-cell leukemia[19,20]. An analysis of the Surveillance, Epidemiology, and End Results Program (SEER) in 2020, examined the rate of SMNs in patients with DLBCL and demonstrated that patients with DLBCL are 5.3 times more likely than the general population to develop a second NHL [21].

Patients treated with CAR T-cell therapy have often been exposed to multiple previous lines of therapy, increasing their risk of developing a SMN; this may include T-cell neoplasms[22,23]. Recently, two large, multi-center retrospective analyses of patients with DLBCL treated with standard-of-care chemoimmunotherapy reported a rate of SMN of 13.3% and 18.7% at a median follow-up of 13 and 20 years, respectively[22,23]. Additionally, one retrospective query of the FDA Adverse Event Reporting System suggested an increased incidence of T-cell related neoplasms in patients previously treated with anti-PD1 check point inhibition [24].

Inhis large retrospective analysis highlights we report the incidence of SMNs (8.2%), and in particular highlight the low incidence of T-cell lymphoma (1 out 549 pts), following anti-CD19 CAR T-cell therapy at a median of 3 years of follow up. The one patient who developed a peripheral T-cell lymphoma in this retrospective patient cohort had a prior smoking history, a pre-existing auto-immune condition, and had been exposed to 3 previous lines on therapy (including immunotherapy) prior to receiving CAR T-cell therapy. Given the increased incidence of lymphoproliferative neoplasms (including T-cell lymphomas) in patients with autoimmune disease and B-cell lymphoma, as well as the increased risk of SMN seen with

previous exposure to chemoimmunotherapy, it is difficult to draw any conclusive link between the development of a T-cell neoplasm in our patient and prior CAR T-cell exposure [13,17].

It should be acknowledged that this retrospective analysis was limited to those patients previously treated with anti-CD19 CAR T-cell constructs and did not include patients treated with anti-BCMA CAR T-cells. Furthermore, a major limitation of our study, as well as the data reported by the FDA, is the limited accountability for competing events such as subsequent lines of therapy or death following CAR T, which may result in an over- or under- estimation of the observed incidence of SMNs in the post CAR T-cell setting and thereby the perceived risks associated with CAR T-cell therapy [14]. It is for this reason we support ongoing discussion and investigation into the development of SMNs post-CAR T. Additionally, we encourage further investigation into CAR T-cell persistence and T-cell subsets in patients who develop T-cell neoplasms following both BCMA- and CD19- directed CAR T-cell therapy as well as molecular analysis to examine the presence of CAR transgenes and remnant viral vector genes. In the interim, it is imperative to weigh risk versus benefit when reviewing this announcement with patients as CAR T-cell therapy continues to provide a curative option in LBCL and a life-saving measure in other hematologic malignancies.

The trial was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at each participating institution.

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Conflict of Interest:

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Table 1. Baseline Characteristics for All Patients

Baseline Characteristics n= 582 (%)		
CAR T-cell Product		
Axi-cel	360 (61.9)	
Tisa-cel	152 (26.1)	
Liso-cel	70 (12.0)	
EBER Positive	17	
HIV Positive*	4	
Autoimmune Disease		
Rheumatoid	6	
Arthritis	4	
SLE	4	
Chron's Disease	1	
Sjogren's Syndrome	1	
Ulcerative Colitis	1	
Psoriatic Arthritis	9	
Other		
Median Prior Lines of Therapy (range)	3 (1-18)	
Prior Stem Cell Transplantation		
Autologous	224 (38.5)	
Allogenic	6 (1.0)	
Best Response to Therapy		
CR	261 (44.8)	
PR	103 (17.7)	
SD	50 (8.9)	
PD	94 (16.2)	
NE	12 (2.1)	

*As reported per institutional policy

Abbreviations- CAR: chimeric antigen receptor, axi-cel: axicabtagene ciloleucel, tisa-cel: tisagenlecleucel, liso-cel: lisocabtagene maraleucel, EBER: Epstein-Barr virus-encoded RNA, HIV: human immunodeficiency virus, SLE: Systemic lupus erythematosus, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable

Table 1. Characteristics of Patients with Subsequent Malignant Neoplasms

Subsequent Malignant Neoplasms (n= 45)	
CAR T-cell Product	
Axi-cel	26 (57.8)
Tisa-celx``	9 (20.0)
Liso-cel	10 (22.2)
Histologic Subtype	
DLBCL	22 (48.9)
Transformed FL	14 (31.1)
PMBCL	1 (2.2)
Richter's	2 (4.0)
Grey Zone	1 (2.2)
Other	3 (6.6)
Molecular Rearrangements by FISH	
C-MYC	6 (13.3)
BCL-2	9 (20.0)
BCL-6	6 (13.3)
Double Hit	3 (6.7)
Prior Tobacco Use	14 (31.1)
EBER Positive	0
HIV Positive*	0
Autoimmune Disease	2 (4.4)
Median Prior Lines of Therapy (range)	3 (2-7)
Prior Stem Cell Transplantation	
Autologous	25 (55.6)
Allogenic	2 (4.4)
Bridging Therapy	n=27
Steroids alone	3 (11.1)
Rituximab +/- steroids	1 (3.7)
Chemotherapy +/- Rituximab or steroids	9 (33.3)
Lenalidomide +/- Rituximab or steroids	2 (7.4)
Obinutuzumab +/- Rituximab or steroids	2 (7.4)
Polatuzumab- BR	4 (14.8)
BTK-I +/- Venetoclax	3 (11.1)
Other	3 (11.1)
Best Response to Therapy	
CR	32 (71.1)
PR	5 (11.1)
SD	1 (2.2)
PD	4 (8.9)
NE	3 (6.7)
Subsequent Malignant Neoplasm	
MDS	18 (40.0)
Solid Tumor	11 (24.4)
AML	6 (13.3)
Cutaneous (BCC/SCC)	5 (11.1)
PTCL	1 (2.2)
Other	4 (8.9)
Median Time from CAR T-cell infusion to SMN (mos, range)	19.3 (4.0- 80.2)

Abbreviations- CAR: chimeric antigen receptor, axi-cel: axicabtagene ciloleucel, tisa-cel: tisagenlecleucel, liso-cel: lisocabtagene maraleucel, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, PMBCL: primary mediastinal B-cell lymphoma, BCL-2: B-cell lymphoma 2, BCL-6: B-cell lymphoma 2, EBER: Epstein-Barr virus-encoded RNA, HIV: human immunodeficiency virus, BR: bendamustine/rituximab, BTKi: bruton tyrosine kinase inhibitor, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable, MDS: myelodysplastic syndrome, AML: acute myeloid leukemia, BCC: Basal cell carcinoma, SCC: squamous cell carcinoma, PTCL: Peripheral T-cell lymphoma, SMN: subsequent malignant neoplasm, mos: months.

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