RESEARCH LETTER

blood advances

TO THE EDITOR:

Subsequent malignant neoplasms in patients previously treated with anti-CD19 CAR T-cell therapy

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Chimeric antigen receptor (CAR) T-cell therapy is a novel therapy that uses either gamma-retroviral or lentiviral vectors to genetically modify a patient's autologous T cells to express an anti-CD19 antibody against $CD19^+$ B-cell malignancies.[1,2] Since 2017, a total of 3 anti-CD19 CAR T-cell therapies, axicabtagene ciloleucel (axi-cel; Yescarta), tisagenlecleucel (tisa-cel; Kymriah), and lisocabtagene maraleucel (liso-cel; Breyanzi), have been approved by the FDA 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) after CAR T-cell therapy and no other subsequent malignant neoplasms (SMNs).[9,10] However, multiple real-world retrospective analyses examining outcomes after treatment with CAR T-cell therapy report varying rates of SMNs ranging from 0.9% to 12.9%, with the most common 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 the 28th of November, 2023, the Food and Drug Administration (FDA) announced an investigation into reports of T-cell malignancies, including CAR-positive lymphomas, in patients who received treatment with B-cell maturation antigen (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 after CAR T-cell therapy, we performed a large retrospective analysis 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 large B-cell lymphoma (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 autologous hematopoietic stem cell transplant (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 (PFS) of 11.5 months (95% confidence interval [CI], 6.08-16.92) and median overall survival (OS) of 27.8 months (95% CI, 21.2-34.5). Seventeen patients had Epstein-Barr virus (EBV) positive disease, 4 had HIV infection, and 26 patients had a previously diagnosed autoimmune condition (Table 1).

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Authors are committed to sharing critical, deidentified data with medical experts and scientific researchers in the interest of advancing public health and access can be requested by contacting the corresponding author, Reem Karmali (reem.karmali@nm.org).

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 arthritis	6
SLE	4
Crohn disease	4
Sjogren syndrome	1
Ulcerative colitis	1
Psoriatic arthritis	1
Other	9
Median prior lines of therapy (range)	3 (1-18)
Prior stem cell transplantation	
Autologous	224 (38.5)
Allogeneic	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)

CR, complete response; EBER, Epstein-Barr virus–encoded RNA; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SLE, systemic lupus erythematosus.
*As reported per institutional policy.

Table 2. Characteristics of patients with SMNs

SMNs (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	2 (4.0)
Gray 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)
Allogeneic	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)
SMN	
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 (range), mo	19.3 (4.0-80.2)

AML, acute myeloid leukemia; BCC, basal cell carcinoma; BCL-2, B-cell lymphoma 2; BR, bendamustine/rituximab; BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; EBER, Epstein-Barr virus–encoded RNA; NE, not evaluable; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; PTCL, peripheral T-cell lymphoma; SCC, squamous cell carcinoma; SD, stable disease.

Data on SMNs were captured in 549 patients. Forty-five (8.2%) of these patients developed an SMN after 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 MDS (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 autologous-HSCT and 2 patients who previously received an allogeneic-HSCT. Additionally, 27 of these patients received bridging therapy before CAR T-cell infusion (regimen details outlined in Table 2). No patients who developed an SMN were EBV positive or HIV positive, and only 2 had preexisting autoimmune conditions. Fourteen patients (31.1%) who developed SMN had a history of prior tobacco use.

Of the 504 patients in our data set who did not develop an SMN, 287 patients relapsed after 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 after 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 after relapsed disease and subsequent lines of therapy, of whom 5 developed a myeloid neoplasm (acute myeloid leukemia, n = 1; MDS, n = 4).

The median follow-up of those patients who developed an SMN was 35 months, at which time the median PFS after CAR T-cell therapy had not been reached. Twenty-nine of the 45 patients with SMNs were alive at the last known follow-up. Of the 16 deceased patients, 8 deaths were attributed to complications or progression of SMN, with a median OS from the 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 gray zone lymphoma (International Prognostic Index of 4) was initially treated with dose adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, and cyclophosphamide) with partial response to therapy. He was subsequently exposed to pembrolizumab with inadequate response and proceeded to CAR T-cell therapy with 1 dose of brentuximab-vedotin as bridge. He received axicabtagene ciloleucel and achieved a complete response but was subsequently diagnosed with both a peripheral T-cell lymphoma, not otherwise specified and a concurrent non–small cell lung cancer ~4 months (121 days) after CAR T-cell infusion. The patient died of non–small cell lung cancer 2 years after receiving CAR T-cell therapy. Unfortunately, genomic sequencing to evaluate the involvement of the CAR T cells in this T-cell neoplasm was not performed because tissue was not accessible.

Patients with a history of immune dysregulation, such as that associated with EBV, HIV, autoimmune disease, or 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% to 5% of cases of NHL, with the most frequent being a combination of LBCL 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 LBCL and demonstrated that patients with LBCL 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, 2 large, multicenter retrospective analyses of patients with LBCL 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, 1 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]

In this large retrospective analysis, we report the incidence of SMNs (8.2%) and, in particular, highlight the low incidence of T-cell lymphoma (1 of 549 patients), after anti-CD19 CAR T-cell therapy at a median of 3 years of follow-up. The patient who developed a peripheral T-cell lymphoma in this retrospective patient cohort had a prior smoking history, a preexisting autoimmune condition, and had been exposed to 3 previous lines on therapy (including immunotherapy) before 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 after CAR T-cell therapy, which may result in an overestimation or underestimation 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] Consequently, we support ongoing discussion and investigation into the development of SMNs after CAR T-cell therapy. Additionally, we encourage further investigation into CAR T-cell persistence and T-cell subsets in patients who develop T-cell neoplasms after 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 vs benefit when reviewing this announcement with patients because 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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