Clonal evolution and the risk of secondary myeloid neoplasia following chimeric antigen receptor T-cell therapy

Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized the management of relapsed/refractory non-Hodgkin lymphoma (NHL).[1] While immune effector-cell-associated hematologic toxicity is the commonest cause of cytopenias after CAR-T therapy, secondary treatment-associated myeloid neoplasms (tMN) have been reported with increasing frequency.[2-5]

tMN is a well-recognized complication of DNA-damaging chemotherapy, classically arising 5-7 years after exposure, and has an extremely poor prognosis (overall survival, <1 year).[6,7] Among NHL patients treated with autologous stem cell transplantation (ASCT), the 10-year incidence of tMN can be as high as 12-24%, with older and heavily pre-treated patients at highest risk.[8,9] Although pivotal CAR-T studies did not initially report tMN as an adverse event, emerging real-world data suggest an incidence of 3-6%.[2,4] In contrast to the post-ASCT experience, patients receiving CAR-T therapy appear to have a short latency between CAR-T infusion and tMN onset, e.g., 3-10 months,[4] compared to 4-5 years after ASCT, and an extremely poor prognosis of only 3-8 months following tMN diagnosis,[4] compared to 13-15 months in the post-ASCT setting. Clonal hematopoeisis of indeterminate potential (CHIP) has been observed in some patients prior to CAR-T therapy and may contribute to tMN risk;[9] additionally, mutations in DNA repair mechanisms have been identified in cases of post-CAR-T tMN.[2,10] Clonal evolution has been identified in several cases of post-CAR-T tMN.[2-3,9]

Identification of risk factors for the development of post-CAR-T tMN is of paramount importance in order to flag high-risk subgroups who may benefit from closer monitoring after CAR-T therapy, and to aid patient counseling prior to such therapy. Here we describe our single-center experience of post-CAR-T tMN in ten NHL patients. Using an age- and sex-matched control group, we identify potential risk factors for tMN, and begin to characterize underlying driver mutations and clonal evolution in this cohort.

Demographics, disease characteristics and baseline CAR-HEMATOTOX (HT) scores, were assessed for ten cases of post-CAR-T myeloid malignancies (tMN) (as defined by the World Health Organiazation 5th edition) arising between 2019-2024 at University College London Hospital (UCLH) and for a 3:1 age- and sex-matched control cohort who received CAR-T therapy at the same hospital but did not develop tMN (*Online Supplementary Figure S1*). RNA sequencing (Archer Pan-Heme FusionPlex NGS) was conducted on samples (blood, bone marrow and lymph nodes) taken before and after CAR-T therapy. Ethical approval for the use of the study data was granted by Derby Research Ethics Committee (reference 24/EM/0221, IRAS project ID 336254).

To assess baseline and post-CAR-T risk factors separately, time to development of tMN was measured as the interval between CAR-T infusion or day 28, respectively, and date of tMN diagnosis, death or date last seen alive using competing risks survival analysis (Fine & Grey) with death (without tMN) included as a competing risk. Associations between number of prior lines of therapy, HT score and ASCT were assessed using linear regression and Wilcoxon Mann-Whitney testing. All analyses were performed in STATA version 18.0 (StataCorp, College Station, TX, USA), with two-sided $P<0.5$ indicating statistical significance.

Among 403 NHL patients infused with CAR-T at UCLH, ten cases of post-CAR-T myeloid malignancies (tMN) were observed (incidence, 2.48%). All patients within this cohort were treated with CD19-directed CAR-T: nine of the ten (90%) cases of tMN had been treated with commercial CAR-T products with CD28 co-stimulatory domains and one patient (10%) had been treated with AUTO-1 containing a 4-1BB co-stimulatory domain (Table 1, *Online Supplementary Table S1*). All patients received standard-intensity lymphodepletion with fludarabine and cyclophosphamide prior to the CAR-T therapy (*Online Supplementary Table S1*). The median age of the ten patients with tMN was 54 years (range, 33-67 years), six were male, disease stage was III-IV in eight, and the median baseline lactate dehydrogenase concentration was 244 U/L (range, 155-462 U/L) (Table 1). Two of the ten patients who developed tMN relapsed with NHL and received further therapy 14 and 16 months after CAR-T therapy (*Online Supplementary Table S1*). tMN was diagnosed at a median of 11.2 months (interquartile range [IQR], 5.2-21.2 months) after CAR-T therapy and included acute myeloid leukemia (N=2) and myelodysplastic syndrome (N=8) with bi-allelic *TP53* inactivation, low blasts or hypoplasia in one, six and one cases, respectively. The median overall survival after the diagnosis of tMN was 8.1 months (IQR, 6.4-24.3 months) and 70% of the tMN cohort are now dead (Figure 1). All these deaths were due to tMN, with two patients having infectious complications (appendicitis, mucormycosis) listed as additional causes of death (*Online Supplementary Table S1*).

In seven of ten cases, pre-CAR-T biopsy material was available to test for baseline CHIP by next-generation sequencing (1/7 pleural biopsy; 3/7 bone marrow; 3/7 lymph

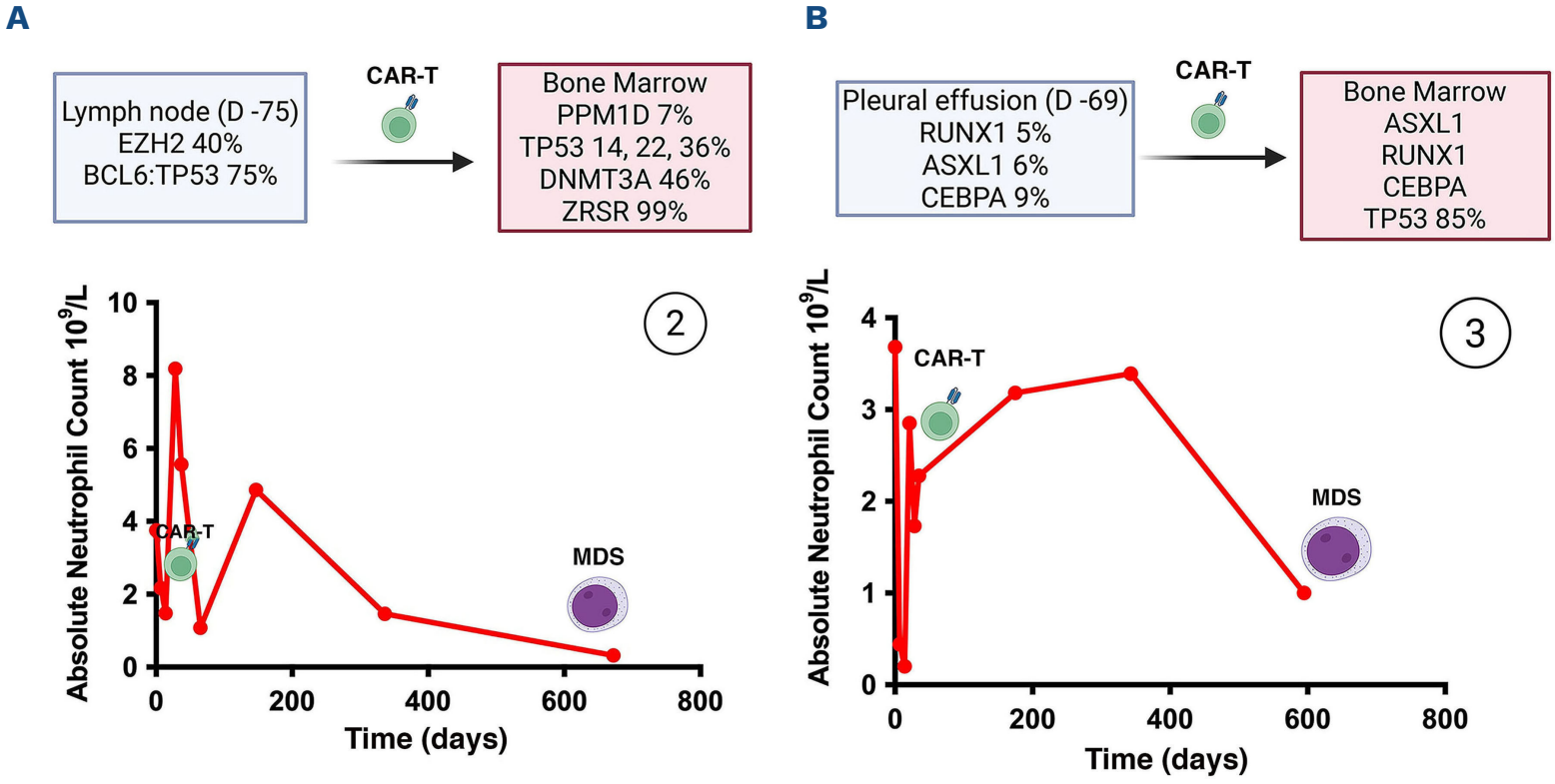
nodes), and pre-CAR-T driver mutations with a variant allele frequency >2%[11] were identified in four of the seven patients (1/4 pleural biopsy; 3/4 bone marrow). These clones included *PPM1D* (2/4), *TP53* (1/4), *TET2* (1/4), *ASXL1* (1/4), *RUNX1* (1/4), and *CEBPA* (1/4), which persisted or increased at tMN diagnosis. In three of the ten patients with detectable non-driver CHIP at baseline, mutations arising at tMN diagnosis were *TP53* (1/3), *DNTM3A* (3/3), *ZRSR* (1/3), *PPM1D* (2/3) and *ASXL1* (1/3); this is illustrated in Figure 1. In three of ten patients without baseline samples or detectable CHIP, mutations in *ASXL1* (2/3), *DNMT3A* (2/3), *RUNX1* (1/3) and *BCOR* (1/3) were identified by bone marrow analysis at tMN diagnosis. We included non bone-marrow tissues such as pleural fluid and lymph node to allow us to demonstrate mutational yield across sample types. Individual patients' characteristerics, including tMN classification, International Prognostic Scoring System risk group and tMN treatment are outlined in *Online Supplementary Table S1*.

All ten (100%) of the patients with post CAR-T tMN had a complete or partial response to the CAR-T therapy at day 100 compared to 26/30 (86.6%) in the control group (P=0.22). Univariable analysis comparing tMN patients to the control cohort (median follow-up, 33.8 months [IQR: 25.5-40.4]; range, 7-50.3 months) identified a significant association between pre-CAR-T factors such as prior ASCT, high baseline HT score (Table 2, *Online Supplementary Figure S2*), and number of prior lines of therapy with risk of post-CAR-T tMN (Tables 1 and 2). The small numbers of

Table 1. Baseline demographics and risk factors of patients treated with chimeric antigen receptor T cells who developed myeloid malignancies after the therapy and of an age-matched control cohort.

Characteristic	Myeloid malignancies N=10	Control N=30
CAR-T product, N (%)		
Axi-cel	8 (80.0)	28 (93.3)
AUTO1	1 (10.0)	0
Brexu-cel	1 (10.0)	0
Tisa-cel	0	2 (6.7)
Age, years, median (IQR), range	54 (50-60) 33-67	55 (49-59) 33-62
Sex, N (%)		
Male	6 (60.0)	18 (60.0)
Female	4 (40.0)	12 (40.0)
Diagnosis, N (%)		
De novo DLBCL	1 (10.0)	20 (69.0)
tFL	4 (40.0)	7 (24.1)
FL	2 (20.0)	1 (3.4)
MCL	1 (10.0)	0
tWM	1 (10.0)	0
tLPL	1 (10.0)	0
PMBCL	0	1 (3.4)
Missing/unknown	0	1
Stage		
0-II	2 (20.0)	8 (26.7)
III-IV	8 (80.0)	22 (73.3)
LDH, N (%)		
<ULN	3 (30.0)	11 (36.7)
≥ULN<2xULN	6 (60.0)	15 (50.0)
≥2xULN	1 (10.0)	4 (13.3)
LDH, IU/L, median (IQR), range	244 (185-312) 155-462	247 (203-286) 163-1,168
CAR-HT score, median (IQR), range	3.5 (2.0-5.0) 0-6	1.0 (0.0-3.0) 0-5
Prior lines of therapy, median (IQR), range	5 (4-5) 3-6	2 (2-3) 2-6
Previous SCT, N (%)		
No	2 (20.0)	23 (76.7)
Autograft	8 (80.0)	6 (20.0)
Autograft and allograft	0	1 (3.3)
Baseline CRP, mg/L, median (IQR), range	9.2 (6.3-13.0) 4.10-47	2.9 (2.1-13.7) 0.5-70.7
CRP peak, median (IQR), range	37.9 (29.4-87.5) 7.90-136.80	62.2 (25.9-161.2) 1.7-284.1
Change in CRP, %, median (IQR), range	572.9 (90.2-717.1) 80.64-2,171.43	1,233.5 (308.9-5,851.3) 120.20-17,666.67
Baseline ferritin, μg/L), median (IQR), range	678.5 (135.0-1,155.0) 30-10,487	532.0 (179.0-1,190.0) 40-1,662
Peak ferritin, μg/L, median (IQR), range	1,298 (1,051-2,312) 154-12,468	1,025 (574-2,080) 90-3,498
Change in ferritin, %, median (IQR), range	261.8 (182.5-545.4) 118.89-853.41	232.9 (139.2-330.7) 41.34-628.75
Lymphocyte count at baseline, x10^9/L, median (IQR), range	0.6(0.4-0.8) 0.18-1.67	0.5(0.4- 0.6) 0.15-1.42
Absolute lymphocyte count post CAR-T, x10^9/L, median (IQR), range	0.4 (0.2-0.5) 0.07-1.07	0.2 (0.1-0.3) 0.02-0.79
Change in lymphocyte count, %, median (IQR), range	38.9 (29.8-91.5) 17.39-254.76	39.0 (24.6- 54.9) 5.56-453.33
Max CRS grade, median (IQR), range	2.0 (1.0-2.0) 1-2	1.0 (1.0-2.0) 0-2
Max ICANS grade, median (IQR), range	0.0 (0.0-0.0) 0-3	0.0 (0.0-0.0) 0-3

CAR-T: chimeric antigen receptor T cells; Axi-cel: axicabtagene ciloleucel; AUTO1: academic CAR-T product (CD19CAT-41BBζ); Brexu-cel: brexucabtagene autoleucel; Tisa-cel: tisagenlecleucel; IQR: interquartile range; DLBCL: diffuse large B-cell lymphoma; t: transformed; FL: follicular lymphoma; MCL: mantle cell lymphoma; WM: Waldenström's macroglobulinemia; LPL: lymphoplasmacytic lymphoma; PMBCL: primary mediastinal B-cell lymphoma; LDH: lactate dehydrogenase; ULN: upper limit of normal; CAR-HT: CAR-HEMATOTOX; SCT: stem cell transplant; CRP: C-reactive protein; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.



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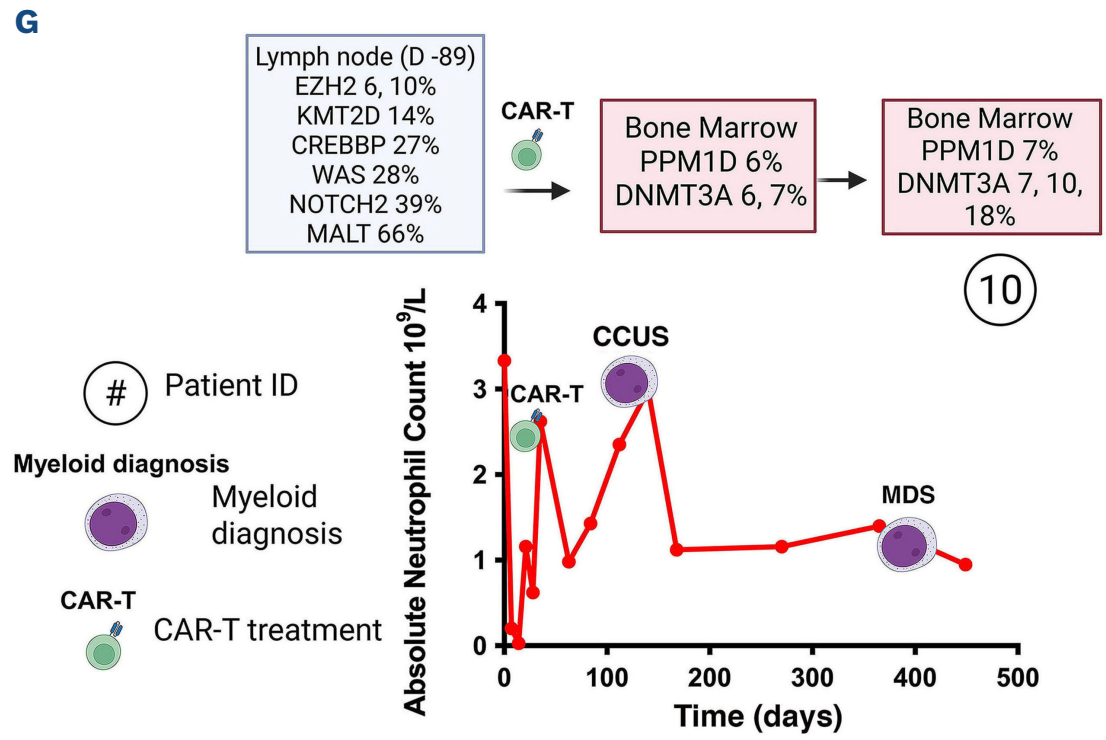

Figure 1. Clonal evolution and characteristics of patients with therapy-associated myeloid neoplasms following chimeric antigen receptor T-cell therapy. (A-G) Ten patients treated with chimeric antigen receptor T cells developed treatment-associated myeloid neoplasms. Clonal evolution over time is plotted against absolute neutrophil count for seven of these ten patients for whom pre- and post-treatment biopsy material was available for evaluation by next-generation sequencing; non-bone marrow tissue is included to describe longitudinal mutational evolution. Time on the x axis relates to number of days since the first mutational analysis. (H) Summary of the clinical course of the ten patients treated with chimeric antigen receptor T cells who developed treatment-associated myeloid neoplasms. CAR-T: chimeric antigen receptor T-cell; D: day; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; CCUS: clonal cytopenia of undetermined signficance.

patients preclude a full multivariable analysis, but pairwise comparisons identified baseline HT score and number of prior lines of therapy as independent risk factors. Thus, for an increase of 1 point in the HT score, the hazard ratio (HR) was 1.47 (95% confidence interval [95% CI]: 1.02-2.14, *P*=0.041), and for one additional line of prior therapy the HR was 2.01 (95% CI: 1.24-3.25; *P*=0.005). In contrast, much of the excess risk from prior ASCT disappeared when adjusted for prior lines of therapy (HR=2.31, 95% CI: 0.36-14.89; *P*=0.38). Higher peak lymphocyte count but not lactate dehydrogenase concentration was significantly associated with tMN (*P*=0.012), with a trend for higher cytokine release syndrome grade (*P*=0.053). There were no associations with peak serum ferritin level, C-reactive protein concentration,

immune effector cell-associated neurotoxicity syndrome grade, or time to neutrophil recovery during month 1.

Published data suggest that tMN affects 3-6% of patients treated with CAR-T and, in this setting, occurs with a short latency and has extremely poor clinical outcomes.[10] Proposed risk factors include advanced age, pre-treatment cytopenia(s),[2] multiple prior treatment lines,[2,10] and the presence of pre-treatment CHIP 'driver mutations' in a subset of patients.[2-3,9] Here, using CAR-T therapy for NHL in the third-line setting, we confirm these observations in ten cases of tMN, demonstrating an overall incidence of 2.48%, short latency (median 7.3 months), and poor median overall survival (8.1 months).

Pre-treatment risk prediction, compared with that for age-matched controls, showed that high baseline HT score and number of prior lines of therapy (including ASCT) are associated with higher tMN risk. Future data on tMN incidence following second-line (and even first-line) CAR-T therapy for NHL will help to determine whether CAR-T therapy drives tMN risk independently of prior treatments. If the tMN signal is lower followng first- or second-line CAR-T therapy, this may further support the use of CAR-T in earlier lines.

In our analysis, peak lymphocyte count (as a surrogate for CAR-T expansion) was significantly associated with increased risk of tMN, while higher cytokine release syndrome grade showed a trend towards increased risk of tMN. Higher HT score at baseline was associated with tMN risk but peak post-infusion ferritin concentration, which is often used as a marker of CAR-T inflammation, was not. While there is a paucity of mechanistic data to explain a pathophysiological link between CAR-T and tMN, it is hypothesized that CAR-T-associated inflammation may play a role, suppressing normal hematopoiesis[12] and provoking persistent cytopenias.[13] RNA sequencing has identified clonally expanded interferon-γ-secreting $CX3CR1^{+}CD8^{+}$ T cells which can suppress normal hematopoiesis.[14] Furthermore, common myeloid CHIP/'first-hit' mutations in the epigenetic regulators *ASXL1*, *TET2*, *DNMT3A* and *JAK2* can reprogram myeloid cells to adopt a 'pro-inflammatory state'. Here, we identified pre-CAR-T driver mutations in 40% of the tMN cohort, of whom 75% had driver mutations in DNA-repair genes; this is reportedly more common in tMN than in *de novo* myeloid neoplasms due to the selective advantage conferred by mutated DNA-repair genes on malignant cells when exposed to cytotoxic chemotherapy.[15] Our cohort was heavily pre-treated, which may synergize with the highly pro-inflammatory environment provoked

Table 2. Univariable analysis of risk factors for post-chimeric antigen receptor T-cell (CAR-T) therapy-associated myeloid neoplasia, separated into pre-CAR-T and post-CAR-T risk factors.

Risk factor	Events/N	HR (95% CI)	*P*
Pre-CAR-T			
Stage at CAR-T approval			
Stage 0-II	2/10	1.00	0.76
Stage III-IV	8/30	1.27 (0.27-5.99)	
Previous autograft			
No	2/25	1.00	0.010
Yes	8/15	7.63 (1.62-35.99)	
Prior lines of therapy	10/40	2.27 (1.48-3.47)	<0.001
CAR-HEMATOTOX score[a]			
Low (0-1)	2/17	1.00	0.065
High (2+)	8/20	4.33 (0.91-20.55)	
Continuous	8/30	1.63 (1.11-2.41)	0.013
Biochemical parameters (pre-CAR-T)[b]			
LDH (for an increase of 225 U/L)	10/40	0.76 (0.27-2.19)	0.61
Ferritin (for an increase of 100 μg/L)	8/35	1.02 (1.00-1.05)	0.055
CRP (for an increase of 5 mg/L)	7/29	1.02 (0.84-1.23)	0.87
Lymphocytes x 10^9/L	10/40	6.45 (1.03-40.40)	0.047
Post CAR-T[c]			
Biochemical parameters[b]			
Ferritin			
Peak (for an increase of 100 μg/L)	10/35	1.02 (1.00-1.04)	0.098
Change[d] (for an increase of 50%)	8/30	1.14 (0.97-1.35)	0.10
CRP			
Peak (for an increase of 5 mg/dL)	9/29	0.98 (0.93-1.03)	0.37
Change[d] (for an increase of 50%)	7/23	0.97 (0.94-1.02)	0.32
Lymphocytes			
Peak (for an increase of 5x10^9/L)	9/39	18.27 (1.89-176.35)	0.012
Change[d] (for an increase of 50%)	9/39	1.41 (0.97-2.05)	0.070
Toxicity			
CRS (max grade)			
0	0/3	-	0.053[e]
1	4/20	-	
2	6/17	-	
ICANS (max grade)			
0	8/23	1.00	0.31[e]
1	1/5	0.76 (0.09-6.05)	

[a]The CAR-HEMATOTOX score is derived from baseline absolute neutrophil count, platelet count and hemoglobin, C-reactive protein (CRP) and ferritin levels. [b]Hazard ratios for continuous variables represent an increase in the number of units quoted, e.g. for LDH this is the increase in risk for an increase of 225 U/L i.e. the uppler limit of normal for LDH. If no number is quoted, this is the hazard ratio for an increase of 1. For all percentage changes, a hazard ratio represents the increase in risk for a 50% increase. [c]Time measured from day 28 to allow peak measurement for biochemical parameters and recording of CRS and ICANS. [d]Adjusted for baseline value. [e]Log-rank test for trend. HR: hazard ratio; 95% CI: 95% confidence interval; CAR-T: chimeric antigen receptor T-cell; LDH: lactate dehydrogenase; ULN: uppler limit of normal; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

by CAR-T and cause a rapid progression to tMN. Through further propagation of a pro-inflammatory bone marrow niche, CAR-T may confer CHIP clones with a proliferative advantage, favoring evolution of pre-existing CHIP to tMN, and potentially explaining how undetected CHIP clones before CAR-T therapy may become clinically apparent after treatment. Consistent with the potential risk posed by inflammation, our analysis suggests that higher peak lymphocyte expansion after CAR-T therapy and, possibly, higher cytokine release syndrome grade are associated with higher tMN risk. In the four patients with detectable pre-CAR-T tMN driver mutations, we observed clonal evolution following CAR-T infusion.

The limitations of this study include small numbers, which preclude multivariable analysis. Due to the matched case-control design we were unable to assess the association of tMN with age or sex. We were also unable to estimate the cumulative incidence of tMN and 2.48% may be an underestimate, particularly in recently infused patients. It will be essential to explore our findings further in large multicenter studies and compare the incidence of tMN with that following other treatment approaches such as ASCT. Mutational data from non-bone marrow tissues could represent lymphoid rather than myeloid CHIP hence confounding interpretations; however, this information was included to describe the longitudinal evolution of mutations and compare mutational yields across sample types.

Our data are of key importance in highlighting patients' characteristics associated with post-CAR-T tMN, which may guide decisions on the timing of CAR-T therapy and enable counseling of patients about risk. Next-generation sequencing screening prior to CAR-T therapy is not standard practice but may be prudent in heavily pretreated patients and those with high baseline HT scores. Those patients identified with CHIP and additional risk factors may benefit from post-treatment surveillance for tMN to allow earlier diagnosis and consideration of allogeneic stem cell transplantation in eligible candidates.

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Contributions

CR, FS and RG designed the project. RB, TM and SP designed and performed the laboratory work. AAK performed the statistical analysis, AR, KC, FS and MO'R compiled the clinical data. FS, AR, KC and CR wrote the manuscript. All authors edited and reviewed the manuscript.

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