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Frequency of secondary T-cell lymphoma in chimeric antigen receptor T-cell naïve B-cell lymphoid-lineage cancers is higher than that reported on chimeric antigen receptor T-cell therapy

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Conflicts of interest disclosure

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Author contributions

CB and CUN conceived the study, gathered the data, and wrote the draft manuscript. CB performed the analyses. CB, CUN, SLP and PB interpreted the data. All authors contributed to and approved the final manuscript.

To the editor:

Chimeric antigen receptor (CAR) T-cell therapies improve clinical outcomes for diffuse large B-cell lymphoma (DLBCL) and other B-cell lymphoid lineage cancers (B-LC).[1-3] Today, more than 27,000 CAR T-cell doses have been administered in the United States.[4] A recent case series identified 22 patients developing T-cell lymphoma (TCL) after CAR T-cell therapy. The Food and Drug Administration (FDA) has issued a warning on all six approved CAR T-cell products based on these findings. For now, the benefits of CAR T-cell therapies seem to outweigh this risk. First reported in a CAR T-cell treated case-series, three of the 22 US CAR T-cell associated TCL cases demonstrated evidence of clonal similarity to the CAR T-cell product, while another large center reports no clonal relationship between the DLBCL and secondary TCL.[5] Further, the crude rate of T-cell malignancies was only 0.1% in FAERS data[6] and 0.1% to 0.2% in two single-center studies.[5, 7] However, such rates typically underestimate the cumulative incidence without accounting for effects of follow-up time, competing risks, frontline chemoimmunotherapy, and increased likelihood of performing new biopsies in this patient population. As such, data on the background risk of TCL among CAR T-cell naïve patients with relapsed or refractory (R/R) DLBCL or other primary B-LC diagnoses are warranted.

In this study, we investigated the cumulative incidence of TCL for CAR T-cell naïve patients with a diagnosis of DLBCL, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM); four B-LCs approved for CAR T-cell therapies by the FDA. Additionally, we assessed the cumulative incidence of TCL in patients with R/R DLBCL considered eligible for CAR T-cell therapy. All data were retrieved from the Danish Lymphoid Cancer Research (DALY-CARE) data resource.[8] We included all Danish patients registered with a diagnosis of DLBCL, MCL, CLL, and MM between Jan 2002 and Feb 2023 for whom pathology notes were available until May 2023. To exclude concomitant B-LC and TCL diagnoses, patients were first considered at risk three month after B-LC diagnosis and followed until TCL, death, or end of follow-up, whichever came first. From Jan 2005, patients with R/R DLBCL after frontline therapy and younger than 70 years were retrospectively considered eligible for CAR T-cell therapy. CAR T-cell therapy was first approved by the Danish Medicines Council in Sep 2023 for patients with early R/R DLBCL younger than 70 years, and all patients in this study are thus CAR T-cell therapy naïve. The study was approved by the Danish Health Data Authority and National Ethics Committee (approvals P-2020-561 and 1804410, respectively).

We included 10,805 patients with DLBCL (C83.3), 1,515 with MCL (C83.1), 13,773 with CLL/SLL (C83.0 and C91.1), and 10,994 with MM (C90.0). After a median follow-up of 8.5 years (interquartile range [IQR] 4.6 to 13.5) from time of diagnosis (Table 1), we identified 127 patients with a secondary biopsy-verified TCL: 36 (28%) with peripheral TCL NOS (C84.4), 28 (22%) with anaplastic large cell lymphoma (C84.6), 27 (22%) with angioimmunoblastic TCL (C86.5), 18 (14%) with mycosis fungoides (C84.0), 8 (6.3%) with cutaneous TCL, NOS (C84.8), and 10 with other TCL. The overall 1-, 2-, and 5-year cumulative incidence of TCL was 0.11%, 0.17%, and 0.28%, respectively. Stratified on disease, the 5-year cumulative incidence of TCL was 0.56% (n=55), 0.30% (n=4), 0.23% (n=29), and 0.07% (n=7) in patients with DLBCL, MCL, CLL, and MM, respectively (Figure 1A). In a subset of 1,051 patients younger than 70 years with R/R DLBCL after frontline therapy, who today could be considered CAR T-cell treatment eligible in Denmark, the 1-year cumulative incidence of TCL from time of relapse was 0.77% (n=8) and plateaued during 5 years of follow-up (Figure 1B). On the other hand, the median overall survival (OS) from time of DLBCL relapse was only 3.8 years (95% confidence interval 3.0 to 4.7 years), despite significantly improved OS in recent years (Figure 2; *P*=0.035). Of note, only 319 (30.4%) RR DLBCL patients received high-dose therapy followed by an autologous stem cell transplant.

In these population-based, CAR T-cell naïve cohorts, the 5-year incidence of TCL from diagnosis of DLBCL was low, but higher than for patients with CLL or MM. For the patients younger than 70 years at time of R/R DLBCL, who would be considered eligible for CAR T-cell therapy today, the cumulative incidence of TCL was 0.74% after one year of follow-up. This is higher than reported in US patients having undergone CAR T-cell therapy (0.14% or 17 cases per 12,394 patients). The crude rate of TCL after CAR T-cell therapy in the US was thus lower compared to the cumulative incidence after just 14 months from time of diagnosis (overall x-intercept for 0.14%) and to the cumulative incidence after 7.5 months from DLBCL diagnosis (Figure 1A; DLBCL x-intercept for 0.14%). Importantly, two large single-center studies have each reported a single clonally unrelated TCL case among 724 (0.14%) and 449 (0.22%) T-cell therapy recipients, which support a very low incidence of secondary TCL after CAR T cell therapies.[5, 7] Our study is limited by the retrospective design and the fact that risk of a second primary malignancy is associated with chemotherapy exposure,[9] while shorter survival in the CAR T-cell naïve R/R DLBCL population reduces the time at risk of a secondary malignancy.[10] However, developing TCL after a diagnosis of DLBCL, CLL, and MM rarely occurs in CAR T-cell treated[6] and naïve patients, whereas CAR T-cell treated children do not develop TCL at all.[11] Among R/R DLBCL patients considered eligible for CAR T-cell treatment, the cumulative incidence of secondary TCL was markedly higher than what has been reported for patients upon CAR T-cell therapy.[6] Although reporting TCL as an adverse event in the case studies from CAR T-cell treated cohorts may occur, the here reported population-based data on the background risk of TCL in comparable patient populations emphasize that the benefits of CAR T-cell therapies greatly outweighs the risk of CAR T-cell derived TCL. Despite improved survival for patients with R/R DLBCL in recent years as a likely result of better patient selection, supportive care and bispecific therapy in randomized clinical trials,[12] we underscore the urgent need for improved therapy in this patient population.

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Table 1

Table 1. Baseline characteristics at time of diagnosis.

Variable	Unit	DLBCL (N=10,805)	MCL (N=1,515)	CLL (N=13,773)	MM (N=10,994)	Total (n=37,087)
Median age [iqr]	Years	69.3 [59.4, 77.3]	70.4 [62.3, 77.9]	71.5 [63.4, 78.7]	71.7 [63.5, 78.7]	71 [62.3, 78.3]
Sex, N (%)	F	4,728 (43.8)	483 (31.9)	5,714 (41.5)	4,840 (44.0)	15,765 (42.5)
	M	6,077 (56.2)	1032 (68.1)	8,059 (58.5)	6,154 (56.0)	21,322 (57.5)
IPI, N (%)	Low	519 (7.1)	185 (15.9)	1,887 (53.2)	1,809 (26.6)	4,400 (23.3)
	Intermediate	3,385 (46.1)	378 (32.5)	1,006 (28.4)	4,241 (62.4)	9,010 (47.8)
	High	3,444 (46.9)	600 (51.6)	526 (14.8)	751 (11.0)	5,321 (28.2)
	Very high	0 (0.0)	0 (0.0)	128 (3.6)	0 (0.0)	128 (0.7)
	missing	3,457	352	10,226	4,193	18,228

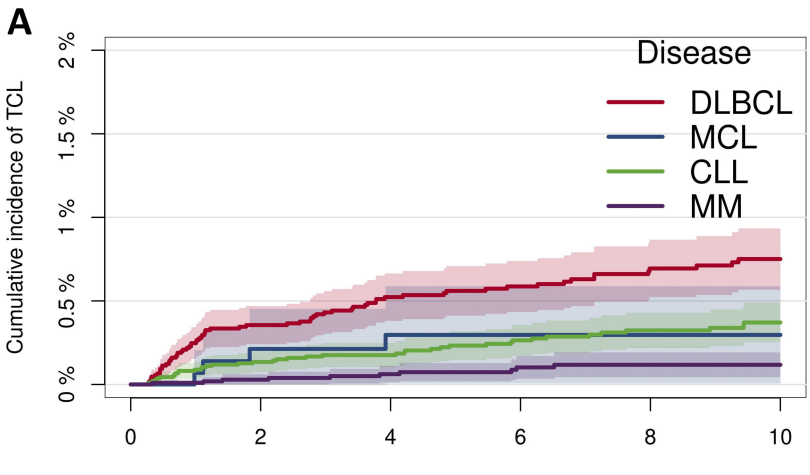
*IPI represents R-IPI in DLBCL, MIPI in MCL, CLL-IPI for CLL, and R-ISS for MM. CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; iqr: interquartile range; IPI: international prognostic index; MCL: mantle cell lymphoma; MM: multiple myeloma.

Figure legends

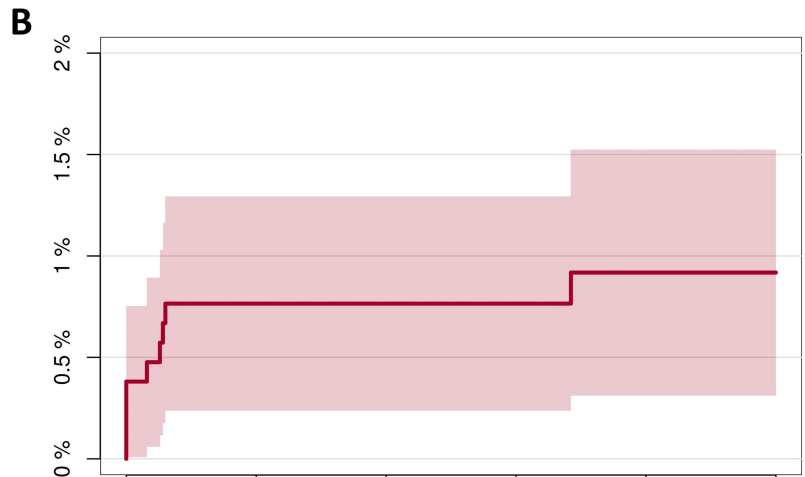
Figure 1. Cumulative incidence of secondary T-cell lymphoma. (A) Cumulative incidence with 95% confidence intervals in patients followed from time of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM), and (B) from time of relapse or refractory DLBCL in patients younger than 70 years. Note that the Y-axis is limited to 2%.

Figure 2. Overall survival from time of DLBCL relapse. (A) Overall survival (OS) in younger patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) from time of relapse. (B) Stratifying patients into three time-periods based on tertile of relapse (i.e. 11 Jul 2005 to 11 Jul 2011 *vs.* 21 Jul 2011 to 28 Jun 2016 *vs.* 11 Jul 2016 to 26 Jan 2023), OS improved significantly in recent years.

FIGURE 1

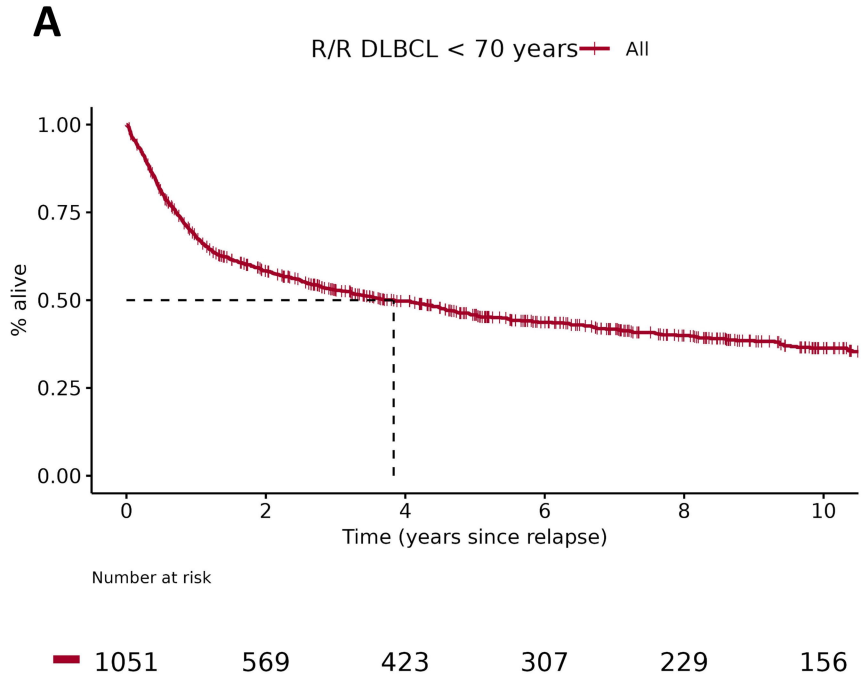


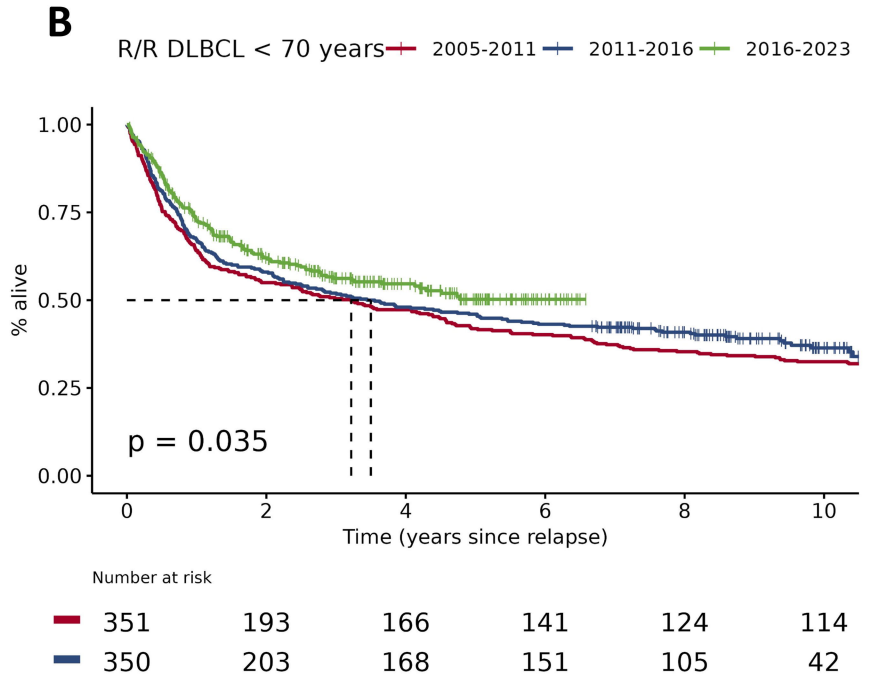
Disease											
DLBCL:	10805	7709	6533	5747	5098	4514	3953	3383	2886	2465	2096
MCL:	1515	1176	985	822	712	609	509	413	333	264	221
CLL:	13773	12109	10676	9352	8128	7036	5981	5004	4189	3407	2753
MM:	10994	8558	7088	5884	4819	3858	3055	2424	1928	1484	1163



R/R											
DLBCL:	1051	689	566	482	422	358	306	267	228	188	155

FIGURE 2


A
R/R DLBCL < 70 years
All
1.00
0.75
0.50
0.25
0.00
% alive
0
2
4
6
8
10
Time (years since relapse)
Number at risk
1051
569
423
307
229
156


B
R/R DLBCL < 70 years
2005-2011
2011-2016
2016-2023
1.00
0.75
0.50
0.25
0.00
% alive
p = 0.035
0
2
4
6
8
10
Time (years since relapse)
Number at risk
351 193 166 141 124 114
350 203 168 151 105 42
350 173 89 15 0 0