Safety of CAR T-cell therapy for cancer in pre-existing autoimmune or inflammatory disease: a retrospective comparative cohort study

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CD19-targeted chimeric antigen receptor (CAR) T-cell therapy is approved to treat some types of relapsed B-cell lymphomas and leukaemias, and B-cell maturation antigen (BCMA)-targeted CAR T-cell therapy is approved to treat relapsed multiple myeloma. A prospective case series of 15 patients who received CD19-targeted CAR T-cell therapy for refractory systemic autoimmune rheumatic diseases showed efficacy, with all reaching drug-free remission.[1] However, 11 of 15 had cytokine release syndrome, and one in 15 had immune-effector cell-associated neurotoxicity syndrome (ICANS), although nearly all adverse events were mild (grade 1).[1] That report had a small sample size, short follow-up, and no comparator group;[1] thus, it is unclear whether patients with autoimmune or inflammatory diseases might have different risks of short-term CAR T-cell therapy side-effects of cytokine release syndrome and ICANS and whether pre-existing autoimmune or inflammatory disease might affect cancer progression after CAR T-cell therapy. Therefore, we investigated safety, cancer progression, and autoimmune or inflammatory disease activity in patients with pre-existing autoimmune or inflammatory disease treated with CAR T-cell therapy for cancer.

In this retrospective cohort study, we identified consecutive patients with and without pre-existing autoimmune or inflammatory disease receiving CAR T-cell therapy for lymphoma or multiple myeloma through routine clinical care at the Dana-Farber Cancer Institute in Boston, MA, USA (October, 2017 to December, 2023). Patients with pre-existing autoimmune or inflammatory disease were identified through medical record review. We did not consider patients who had paraneoplastic autoimmune diseases or immune-related adverse events in the autoimmune or inflammatory disease group. The majority (41 of 53) of patients had their autoimmune or inflammatory disease diagnosed before cancer. The study was approved by the institutional review boards of Mass General Brigham and the Dana-Farber Cancer Institute.

We collected data on demographics; cancer type, stage, duration, and therapies; and autoimmune or inflammatory disease characteristics before and after CAR T-cell therapy. We investigated presence and severity of cytokine release syndrome and ICANS using logistic regression and progression-free survival and overall survival using Cox regression. Multivariable models included age, sex, calendar year, cancer stage, and lymphoma type. Kaplan-Meier curves were also constructed for progression-free survival and overall survival by pre-existing autoimmune or inflammatory disease status with log-rank tests to compare the curves. We did separate analyses for lymphoma and multiple myeloma. In those with autoimmune or inflammatory disease, we compared immunosuppression use, flare, and disease activity in the year before versus after CAR T-cell therapy using paired McNemar's tests.

Of 499 patients with lymphoma who received CD19-targeted CAR T-cell therapy, 47 (9%) had pre-existing autoimmune or inflammatory disease (appendix pp 3–4). In 105 patients with multiple myeloma who received BCMA-targeted CAR T-cell therapy, six (6%) had pre-existing autoimmune or inflammatory disease (appendix p 5). Thus, among both cancers, there were 53 unique patients with pre-existing autoimmune or inflammatory disease. 12 (23%) of 53 patients had a rheumatic disease, and the most common individual disease was psoriasis (ten [19%]; appendix pp 6–7). In those with lymphoma, the most common type was diffuse large B-cell lymphoma (26 [55%] of 47).

See Online for appendix

In patients with lymphoma, cytokine release syndrome occurred in 37 (79%) of 47 with and 377 (83%) of 452 without pre-existing autoimmune or inflammatory disease (multivariable odds ratio [OR] 0·71, 95% CI 0·33–1·51; table). Severe cytokine release syndrome (≥grade 3)[2] occurred in 21 (5%) of 452 patients without autoimmune or inflammatory disease; it did not occur in any patients with autoimmune or inflammatory disease. Tocilizumab use for cytokine release syndrome was not different between groups. ICANS occurred in 26 (55%) of 47 with and 224 (50%) of 452 without pre-existing autoimmune or inflammatory disease (OR 1·20, 95% CI 0·64–2·22). There was no difference in severe ICANS, which occurred

	Events/N (%)	Unadjusted OR (95% CI)	Multivariable* OR (95% CI)
Cytokine release syndrome			
No autoimmune or inflammatory disease	377/452 (83%)	1·0 (ref)	1·0 (ref)
Pre-existing autoimmune or inflammatory disease	37/47 (79%)	0·74 (0·35–1·54)	0·71 (0·33–1·51)
Tocilizumab use for cytokine release syndrome			
No autoimmune or inflammatory disease	276/452 (61%)	1·0 (ref)	1·0 (ref)
Pre-existing autoimmune or inflammatory disease	27/47 (57%)	0·86 (0·47–1·58)	0·80 (0·43–1·49)
Maximum cytokine release syndrome ASTCT ≥grade 3			
No autoimmune or inflammatory disease	21/452 (5%)	1·0 (ref)	1·0 (ref)
Pre-existing autoimmune or inflammatory disease	0/47 (0%)	†	†
ICANS			
No autoimmune or inflammatory disease	224/452 (50%)	1·0 (ref)	1·0 (ref)
Pre-existing autoimmune or inflammatory disease	26/47 (55%)	1·26 (0·69–2·31)	1·20 (0·64–2·22)
Maximum ICANS ACSCT ≥grade 3A			
No autoimmune or inflammatory disease	103/452 (23%)	1·0 (ref)	1·0 (ref)
Pre-existing autoimmune or inflammatory disease	9/47 (19%)	0·80 (0·38–1·71)	0·72 (0·33–1·57)

ASTCT=American Society for Transplantation and Cellular Therapy. ICANS=immune effector cell-associated neurotoxicity syndrome. OR=odds ratio. *Adjusted for age, sex, race, lymphoma type (large B-cell or other), stage (IV or other), and calendar year. †Unable to be estimated due to no events among patients with pre-existing autoimmune or inflammatory disease.

Table: **ORs for cytokine release syndrome and ICANS after CD19-targeted CAR T-cell therapy for lymphoma, comparing patients with and without pre-existing autoimmune or inflammatory disease**

in nine (19%) of 47 of those with and 103 (23%) of 452 without pre-existing autoimmune or inflammatory disease (OR 0·72, 95% CI 0·33–1·57). Results were similar in patients with multiple myeloma after BCMA-targeted CAR T-cell therapy (appendix p 8).

During median follow-up of 9·4 months, there were 208 lymphoma progression events and 164 deaths. There was no association of pre-existing autoimmune or inflammatory disease with progression-free survival (multivariable hazard ratio [HR] 1·18, 95% CI 0·77–1·81) or overall survival (HR 1·53, 95% CI 0·97–2·40; appendix pp 9–10) compared with those without autoimmune or inflammatory disease. Results were similar in patients with multiple myeloma (appendix pp 8, 13) and in secondary analyses stratifying by systemic immunosuppressive medications and in those with large B-cell lymphoma (appendix pp 11–12, 14–18).

Of the 62 individual autoimmune or inflammatory diseases across 53 unique patients, there were nine disease flares in the year before receiving CAR T-cell therapy. There was less systemic immunosuppression medication use (13% *vs* 25%; p=0·008), fewer autoimmune or inflammatory disease flares (2% *vs* 15%; p=0·01), and more patients were in remission or had low disease activity (98% *vs* 85%; p=0·005) in the year after CAR T-cell therapy versus the year before therapy (appendix pp 19–24). Individual-level details on diseases and medications are in the appendix (pp 25–26). Only one patient had a documented autoimmune or inflammatory disease flare after CAR T-cell therapy—mild psoriasis treated with topical steroids 168 days after axicabtagene–ciloleucel (appendix p 27).

A previous study[3] used commercially aggregated electronic health record data and diagnosis codes to identify systemic autoimmune rheumatic diseases and lymphoma treated with CD19-targeted CAR T-cell therapy and found no increased risk of cytokine release syndrome, ICANS, lymphoma progression, or death, similar to our results. However, that study did not have access to health record data so might have inaccuracies.

There are some limitations to consider. First, the pre-existing autoimmune or inflammatory disease group was comprised of several heterogeneous diseases with small sample size, particularly for specific diseases. For example, the most common disease was psoriasis (n=10), followed by Hashimoto's thyroiditis (n=6). Collectively, there were 12 unique patients with rheumatic diseases. However, this number is larger than many previous CAR T-cell therapy studies for autoimmune or inflammatory diseases, and the availability of a comparison group is a strength. Our study includes diseases not previously reported to have received CAR T-cell therapy and is one of the first to report autoimmune and inflammatory outcomes after BCMA-targeted CAR T-cell therapy.[4] Second, few patients had an active autoimmune or inflammatory disease at the time of CAR T-cell therapy. Patients with active autoimmune or inflammatory disease might not have been offered CAR T-cell therapy for cancer due to the possibility of immunosuppressants blunting CAR T-cell therapy efficacy or perceived risk of severe cytokine release syndrome or ICANS or other outcomes such as infection. Third, specific CD19-targeted CAR T-cell products might have differences.[5] In this study, the short-term side-effects of cytokine release syndrome and ICANS might be due to tumour burden rather than autoimmune or inflammatory disease activity. Thus, the results are not directly applicable to prospective trials to treat active autoimmune disease. However, our findings provide reassurance for CAR T-cell therapy outcomes for

patients with cancer with autoimmune or inflammatory diseases.

Fourth, validated measures of autoimmune or inflammatory disease activity were unavailable in this retrospective study. In addition, autoantibodies and other laboratory biomarkers of autoimmune or inflammatory diseases were not routinely measured in these patients so we are unable to investigate levels before and after CAR T-cell therapy. There was only one autoimmune or inflammatory disease flare after CAR T-cell therapy, a novel finding considering our study has longer follow-up than the previous report.[1] Fifth, we only investigated CAR T-cell therapy targeting CD19 or BCMA, so other antigen targets being pursued might have differences.[6] Sixth, in the case-only analysis examining autoimmune or inflammatory outcomes before and after CAR T-cell therapy, we were limited by small sample size and insufficiency of data on time-varying factors, such as concomitant medications, lifestyle, and laboratory results that might have influenced results. Seventh, we were unable to examine other outcomes such as infection, cytopenias, and hypogammaglobulinaemia that can be side-effects of CAR T-cell therapy.[7] In addition, there is concern for risk of CAR T-cell therapy-induced malignancy.[8,9] Lastly, this study was performed at a single centre, so might not be generalisable. However, patients in the study had similar age and proportion of men, though lower racial diversity, compared with a nationwide CAR T-cell therapy study.[10] Currently, nearly all patients receive CAR T-cell therapy at specialised cancer centres like in this study.

In conclusion, patients with pre-existing autoimmune or inflammatory disease had similar safety and cancer outcomes after CAR T-cell therapy as those without autoimmune or inflammatory disease. Autoimmune or inflammatory disease flares occurred less frequently after CD19 or BCMA CAR T-cell therapy and required treatment less often than before CAR T-cell therapy. These findings provide reassurance around the safety of CAR T-cell therapy for patients with cancer with autoimmune or inflammatory diseases and inform ongoing prospective studies of CAR T-cell therapy to treat these patients.

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