haematologica
Journal of the Ferrata Storti Foundation

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Received: January 19, 2026.
Accepted: January 28, 2026.

Citation: GuiZhen Chen and Rahul Banerjee. Post-CAR-T lymphocytosis in multiple myeloma: too much of a good thing?
Haematologica. 2026 Feb 5. doi: 10.3324/haematol.2025.300428 [Epub ahead of print]

Post-CAR-T lymphocytosis in multiple myeloma: too much of a good thing?

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Keywords: Multiple myeloma, CAR-T therapy, lymphocytosis, neurotoxicity

Relevant counts:

Acknowledgments: None.

Funding: Not applicable.

Author contributions: G.C. and R.B. wrote the first draft of the manuscript together and approved the final manuscript.

Data sharing statement: Not applicable.

Competing interests: **R.B**. reports consulting: Abbvie, Adaptive Biotech, BMS, Caribou Biosciences, Genentech, Gilead, GSK, Janssen, Karyopharm, Legend Biotech, Pfizer, Sanofi, SparkCures; Research: Abbvie, BMS, Gilead, Janssen, Novartis, Pack Health, Prothena, Sanofi. The remaining authors have no conflicts to disclose.

In this edition of *Haematologica*, Chai and colleagues describe the results of correlative analyses of patients with multiple myeloma (MM) receiving B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cell therapy.[1] Their study focuses on the intersection of lymphocytosis [as manifested by an elevated peripheral blood absolute lymphocyte count (ALC)], CAR T-cell expansion, and the development of movement/neurocognitive treatment-emergent adverse events (MNTs) including cranial nerve palsies and parkinsonism. Beyond confirming the association between elevated ALC and MNTs as seen in other real-world studies,[2-7] the authors further elucidate specific T-cell phenotypic risk factors for MNT development within the broad category of post-CAR-T lymphocytosis.

MNTs following CAR T-cell therapy in MM were first formally characterized in 2022 as a novel toxicity of ciltacabtagene autoleucel (cilta-cel).[8] More recently, cases have been identified following idecabtagene vicleucel (ide-cel) as well.[9] The mechanism of these MNTs remains incompletely characterized but, in some cases, may, represent off-tumor on-target activity within the basal ganglia.[8,9] Until recently, high tumor burden before CAR T-cell infusion remained the only well-characterized risk factor for MNT development.[8] In contrast, elevated ALC remained (and remains) a proven biomarker of improved outcomes following BCMA CAR T-cell therapy.[10,11] Until last year, many of us would have congratulated patients with robust lymphocytosis following infusion – or even marveled with our own eyes at reactive lymphocytes visible on peripheral smears in some recently infused patients (as visualized by Chai and colleagues in the accompanying article).[1]

This sentiment changed rather abruptly in the past year after a growing number of real-world analyses demonstrated an association between elevated ALC and subsequent MNT development: most typically, in patients with maximum ALC (ALC_{max}) levels over 3.0 thousand cells per microliter ($10^3/\mu L$) in the weeks following CAR T-cell infusion.[2-7] Despite its reasonable

specificity, however, the positive predictive value of $ALC_{max} > 3.0 \times 10^3/\mu L$ in real time has consistently fallen below 50% in real-world data (Table 1). Can we build upon ALC thresholds to better identify patients at the highest risk of MNTs? While the relatively small analysis by Chai and colleagues cannot answer this question definitely, they identify several additional risk factors that require prospective validation. Firstly, regardless of ALC_{max}, patients where CAR T cells (as identified using flow cytometry) comprised over 60% of all circulating T cells were at significantly higher risk of MNT development. Secondly, patients with CD4-predominant CAR T-cell expansion had a higher risk of MNTs than patients with CD8-predominant CAR T-cell expansion; this included one patient with CD4-predominant CAR T-cell expansion within cerebrospinal fluid.[1] This latter finding aligns with analyses from an independent cohort, where interestingly CD4-positive CAR T cells had higher BCMA-binding avidity than CD8-positive CAR T cells.[12]

To be clear, these ALC_{max} details and T-cell phenotypes do not negate the impact of previously identified factors such as tumor burden. In a recently presented analysis of over 750 cilta-cel recipients, both non-response to bridging as well as ALC_{max} over $3.0 \times 10^3/\mu L$ were independent predictors of parkinsonism (n=22 altogether) in multivariable analyses.[6] Similarly, in a separate single-center analysis, elevated ferritin (but not elevated C-reactive protein) was a significant predictor of MNT development.[7] In reality, all of these risk factors likely reflect different aspects of the same multifaceted process: namely, CAR T cells binding too many BCMA-positive cells (whether lymphoid-lineage or not) and expanding too rapidly in response. Further prospective studies will build on these small analyses to build better risk-stratification models beyond reliance on dichotomized lymphocytosis thresholds alone.

Importantly, the above-described research into MNT risk factors cannot conclude whether these risk factors are modifiable in real time. This principle applies most specifically to ALC_{max}, where

many centers have recently begun to employ dexamethasone preemptively (even in the absence of cytokine release syndrome or other symptomatic toxicities) in the setting of rapid post-cilta-cel lymphocytosis. This empiric approach, while understandable given the stark morbidity of MNTs such as parkinsonism, has yielded conflicting results with the limited data we have available so far.[5,13] Furthermore, in the absence of longer follow-up, it is not yet clear that preemptive dexamethasone is risk-free in terms of compromising CAR T-cell expansion or efficacy down the line. As studies of ALC-guided interventions including preemptive dexamethasone continue, we encourage the reporting of subgroup results by other relevant risk factors if possible: for example, response to bridging, CD4:CD8 ratios among CAR T cells, and CAR T expansion as a subset of lymphocytosis (Figure 1). Ultimately, ALC_{max} in isolation may constitute part but not all of the puzzle with regard to why MNTs develop.

In conclusion, while Chai and colleagues have identified certain T-cell phenotypes that predict when MNTs may occur, we still do not completely understand why they occur following BCMA CAR T-cell therapy. More importantly, we still do not know whether lymphocytosis-oriented interventions can truly turn the tide with regard to MNT risk reduction. CAR T-cell expansion *in vivo*, as measurable to some extent via longitudinal ALC kinetics, remains the *sine qua non* of these “living drugs” without which meaningful or durable anti-MM efficacy would be impossible. However, it has become clear that rapid rises in certain CAR T-cell subsets may predispose patients to MNTs that can substantially impair their subsequent quality of life. With further research and validation, we hope that risk-stratification models and preemptive intervention strategies of the future will decrease the incidence of parkinsonism from 6% (in CARTITUDE-1) to 0.6% (in CARTITUDE-4) all the way to zero in coming years.

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Table 1: Selected analyses of MNT development based on peak ALC

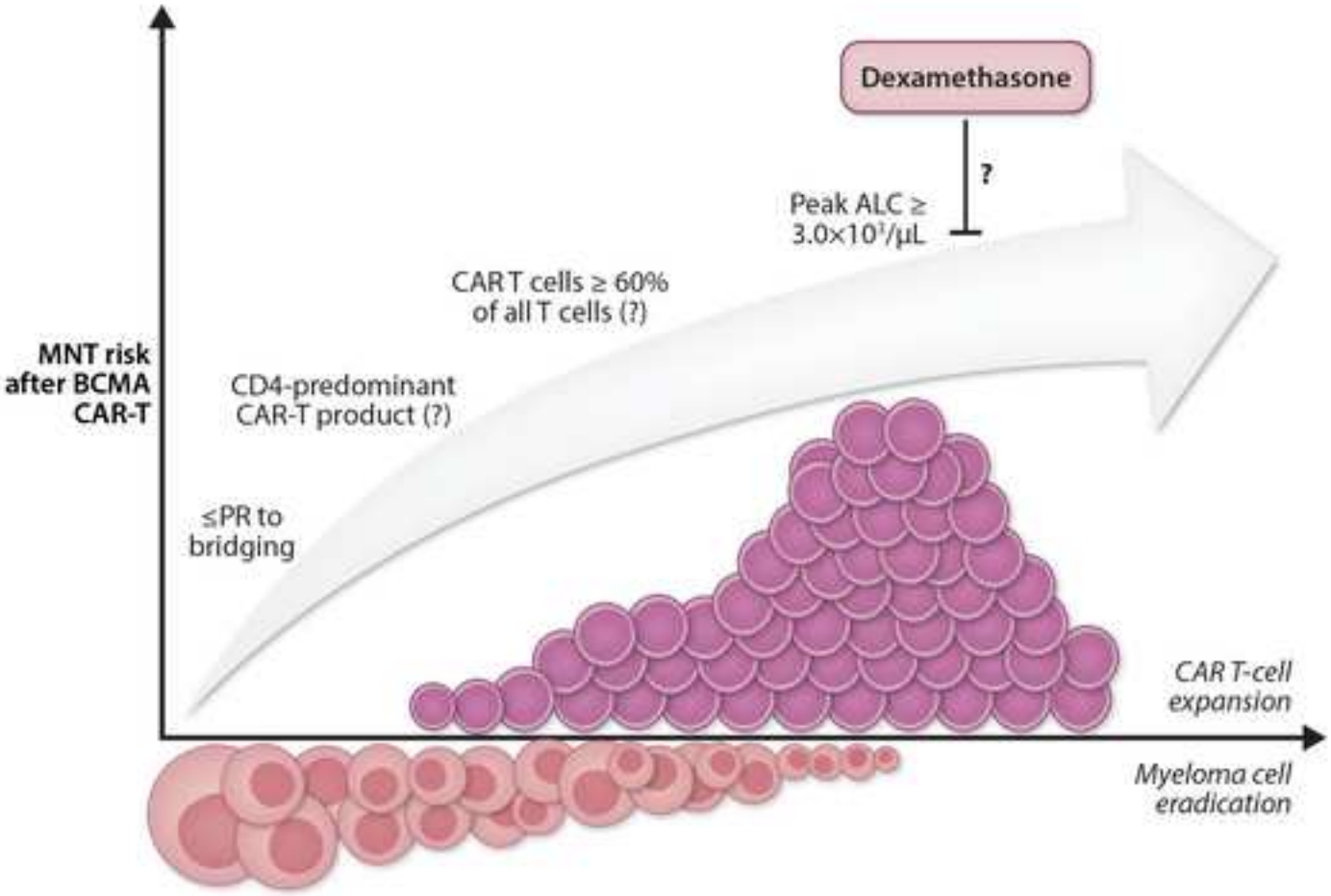
	ALC > 3.0 × 10^3/μL	
	Yes	**No**
Chai 2025[1]	33% (4/12)	0% (0/9)
Lim 2025[2]	29% (19/65)	3% (3/104)
Hosoya 2025[3]	14% (15/104)	4% (6/152)
Jeon 2025[4]	40% (8/20)	10% (6/62)

For the analysis by Jeon and colleagues, the ALC value at D+10 was analyzed shown here; for the other studies, the maximum ALC value was analyzed.

Abbreviations: ALC, absolute lymphocyte count; 10^3/μL, thousand cells per microliter; MNT, movement and neurocognitive treatment-emergent adverse events (including cranial nerve palsies and parkinsonism).

Figure 1: Risk factors for MNT development

Abbreviations: ALC, absolute lymphocyte count; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T-cell; MNT, movement and neurocognitive treatment-emergent adverse events (including cranial nerve palsies and parkinsonism); PR, partial response.


Dexamethasone
?
Peak ALC ≥
3.0×10³/μL
CAR T cells ≥ 60%
of all T cells (?)
MNT risk
after BCMA
CAR-T
CD4-predominant
CAR-T product (?)
≤PR to
bridging
CAR T-cell
expansion
Myeloma cell
eradication