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

GuiZhen Chen[1] and Rahul Banerjee[1,2]

[1]Department of Medicine, University of Washington and [2]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA

Correspondence: R. Banerjee
rahul.banerjee.md@gmail.com

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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 (MNT) including cranial nerve palsies and parkinsonism. Beyond confirming the association between elevated ALC and MNT 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.

MNT 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 MNT 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 their 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 $3.0\times10^3/\mu L$ in the weeks following CAR T-cell infusion.[2-7] Despite its reasonable specificity, however, the positive predictive value of ALC_{max} over $3.0\times10^3/\mu L$ 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 MNT? While the relatively small analysis by Chai and colleagues cannot answer this question definitely, they did identify several additional risk factors that require prospective validation. Firstly, regardless of ALC_{max}, patients whose 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 MNT 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 last finding aligns with analyses from an independent cohort, in which, 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

Table 1. Selected analyses of development of movement and neurocognitive treatment-emergent adverse events (including cranial nerve palsies and parkinsonism) based on peak absolute lymphocyte count.

Authors	ALC >3.0×10³/μL	
	Yes, % (N/N)	No, % (N/N)
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 day +10 was analyzed and is shown here; for the other studies, the maximum ALC value was analyzed. ALC: absolute lymphocyte count.

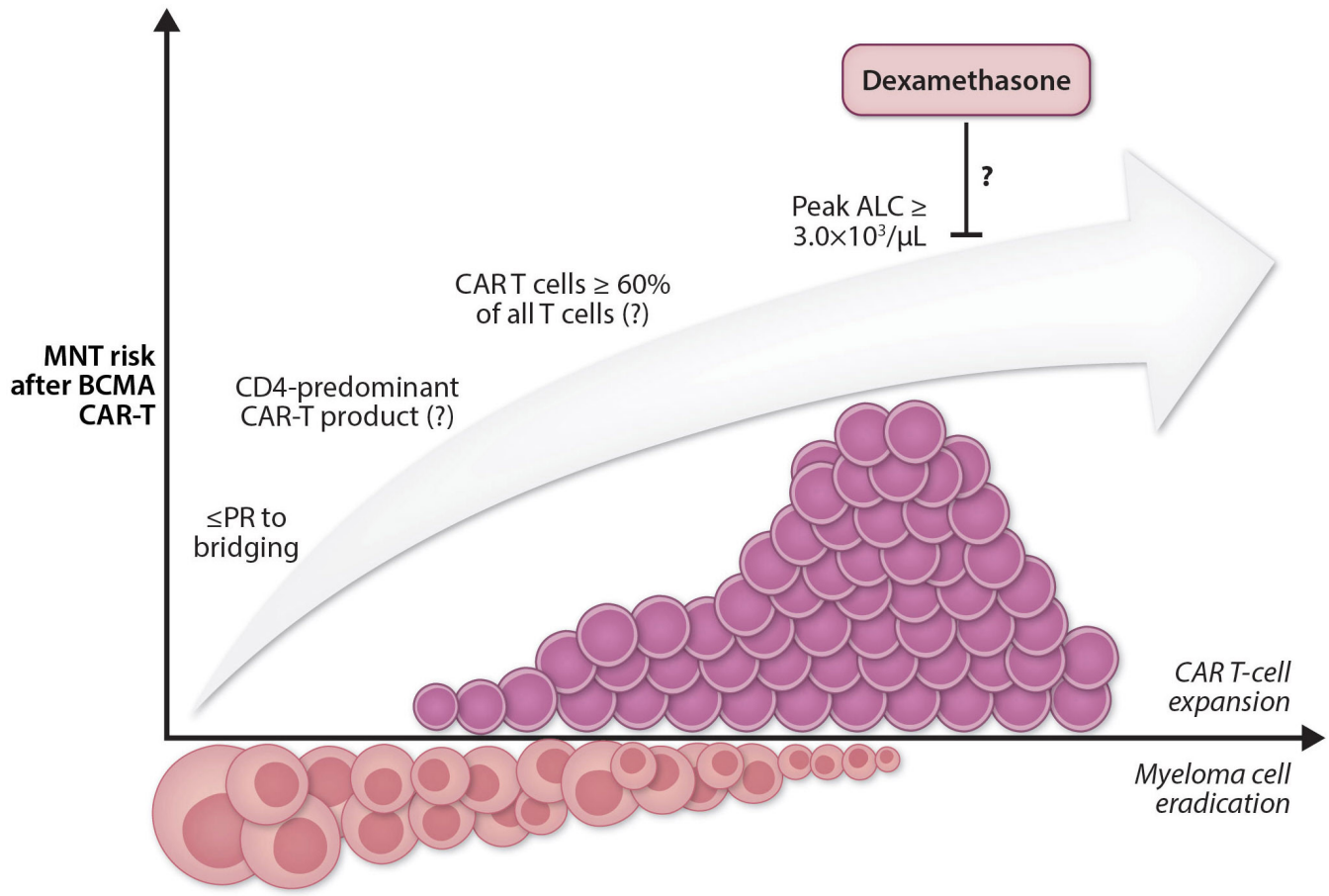

Figure 1. Risk factors for the development of movement and neurocognitive treatment-emergent adverse events. MNT: movement and neurocognitive treatment-emergent adverse events (including cranial nerve palsies and parkinsonism); BCMA: B-cell maturation antigen; CAR-T: chimeric antigen receptor T-cell; PR: partial response; ALC: absolute lymphocyte count.

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 $3.0\times10^3/\mu L$ 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 expand 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 MNT 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 MNT develop.

In conclusion, while Chai and colleagues have identified certain T-cell phenotypes that predict when MNT 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 MNT 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.

Disclosures

RB reports consulting for AbbVie, Adaptive Biotech, BMS, Caribou Biosciences, Genentech, Gilead, GSK, Janssen,

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Contributions

GC and RB wrote the first draft of the manuscript together and approved the final version.

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