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CLINICAL TRIALS AND OBSERVATIONS

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Immunotherapy: the teclistamab fitness test

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In this issue of *Blood*, Cortes-Selva et al[1] perform the most comprehensive analysis to date of the relationship between baseline immune fitness and response to teclistamab in multiple myeloma (MM).

Teclistamab is a bispecific antibody that targets the plasma cell antigen B-cell maturation antigen (BCMA) on 1 arm and stimulates T cells through the signaling molecule CD3 on the other arm. Teclistamab is a first-in-class drug to enter the therapeutic arsenal against MM. In MM, malignant plasma cells proliferate in the bone marrow (BM), leading to bone erosion, anemia, immune suppression, and end-organ damage due to deposition of monoclonal immunoglobulins. Current combination therapies can send MM into remission at early stages of the disease, but with each recurrence, new drug resistances arise, highlighting the pressing need for new treatments.

MM elicits a weak antitumor immune response. Numerous studies have highlighted an essential role for immune surveillance in the control of early stages of MM[2]; thus, this state of relative hyporesponsiveness appears to be acquired during the evolution of the disease. To date, attempts with checkpoint blockade immunotherapy have failed to reinvigorate the immune system of patients with MM.[3]

This context explains why, by bridging gaps in the existing immune response to cancer, enhancement immunotherapy has recently revolutionized the care of patients with MM. Indeed, because bispecific antibodies work by creating an artificial immune synapse between cancer cells and T cells, they do not rely on T-cell antigen specificity, but rather on the presence of T cells poised to destroy a target on stimulation.

Teclistamab was approved in 2022 for patients with relapsed or refractory MM who have received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. This decision was motivated by the results of the phase 1/2 study MajesTEC-1, which reported an overall response rate of 63%, with a median response duration of 18.4 months.[4]

Here, the authors analyzed the immune composition of peripheral blood and BM at the time of screening in 165 patients with MM enrolled in the MajesTEC-1 study. Using both traditional flow cytometry and cytometry by time of flight, they found that the baseline T-cell landscape of responders is critically different from that of nonresponders. Specifically, they report that in both the circulation and the BM, responders had a higher frequency and absolute count of T cells, and particularly cytotoxic CD8 T cells. Both tissues contained a reduced proportion of regulatory T cells (Tregs), especially $CD38^+$ Tregs, in responders. These findings are consistent with the analysis of a small subset of patients who were part of a larger real-world study of teclistamab efficacy, which reported higher CD8 effector T cells in responders.[5] Given the expected greater heterogeneity of real-world patient populations, the reproducibility of this finding carries a considerable weight.

In addition to cytotoxic T cells, response to teclistamab may also require a functional reserve of a less differentiated population: naïve T cells were more abundant in both the blood and the BM of responders. Consistently, the coexpression of the inhibitory receptors PD-1 and Tim3 was lower in responders, indicating that a terminally differentiated, exhausted phenotype might indicate a limited pool of T cells able to respond and reject the tumor.

The authors also analyzed factors related to the other arm of the bispecific antibody, BCMA availability. Surprisingly, they did not find a relationship between response and global as well as per-cell expression of membrane-bound BCMA. Soluble BCMA (sBCMA) instead appeared to be higher in nonresponders. To test whether this finding represents an epiphenomenon of high tumor burden, the authors performed a binomial logistic regression analysis to explain response as a function of multiple indicators of high-risk disease, such as percentage of BM plasma cells, disease stage, and extramedullary disease. Importantly, they found that only sBCMA was associated with poor response. Considering that a previous pharmacokinetic study suggests that sBCMA does not act as a sink for teclistamab,[6] future work will need to clarify whether there is a causal link between sBCMA and teclistamab efficacy.

Finally, the authors asked whether baseline immune characteristics also predict progression-free survival (PFS; with a median of 11.3 months). By performing a multivariate Cox regression analysis, they found that BM $CD25^+$ (activated) CD4 T cells were associated with improved PFS.

The encouraging results of the MajesTEC-1 trial, together with a growing number of real-world studies, support the future use of teclistamab in patients with MM with less advanced disease. Nevertheless, to choose teclistamab over other available treatments, one would need to select the patients most likely to respond. The data presented here offer some hope that it will be possible to do so based on sBCMA and immunologic parameters. Nevertheless, 15 years of research and clinical practice with anti-PD1 immunotherapy in a growing number of cancers offer us a word of caution. To date, no baseline immune characteristic is used to decide which patients to treat with anti-PD1, a decision that considers instead tumor PD-L1 expression and mutational burden. This state of affairs highlights the challenges of going from exploratory analyses to clinically validated biomarkers. Further studies like the one described here, as well as careful meta-analyses, are necessary to rise to these challenges. One important difference between checkpoint blockade immunotherapy and T-cell engagers, like teclistamab, is that the efficacy of the former relies on optimal T-cell stimulation by tumor antigens. To date, measuring the degree of tumor antigen specificity of a T-cell population by a simple, clinically applicable proxy remains difficult. Theoretically, bispecific antibodies, such as teclistamab, can elicit tumor destruction by T cells of any specificity. Therefore, the presence of cytotoxic CD8 T cells in the BM could be sufficient to identify patients with MM poised to respond. Nevertheless, recent data[7] suggest that tumor-specific T cells are still better equipped to translate teclistamab stimulation into treatment response. Therefore, further studies will also need to address this additional layer of complexity of the immune fitness of patients with MM.

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LYMPHOID NEOPLASIA

Comment on Kim et al, page 629

CARs vs bispecifics: the race is on!

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In this issue of *Blood*, Kim and colleagues report on a timely meta-analysis comparing the safety and efficacy of chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies for relapsed/refractory large B-cell lymphoma in the third-line setting and beyond.[1] Pooled complete remission and progression-free survival rates were significantly better for CAR T cells than for bispecific antibodies, although this greater efficacy came with an increased incidence of adverse events (including cytokine release syndrome, neurotoxicity, and infections) in the CAR T group (see figure).

The knowledge that CD19-targeting CAR T-cell therapy can potentially cure patients with relapsed/refractory large B-cell lymphoma approximately 40% of the time[2] with just one treatment motivates clinicians and patients to obtain CAR T-cell therapy, despite the known, often severe side effects that are usually reversible with optimal and immediate management. Axicabtagene ciloleucel,[2] tisagenlecleucel,[3] and lisocabtagene maraleucel[4] have been approved by the US Food and Drug Administration for relapsed/refractory large B-cell lymphoma in the third-line setting and beyond, whereas axicabtagene ciloleucel and lisocabtagene maraleucel are approved for the second-line setting as well. Unfortunately, factors such as disease kinetics, patient comorbidities, socioeconomic/geographic limitations, and resource allocations often make it difficult for CAR T-cell therapy to be used widely.

Bispecific antibodies are an off-the-shelf way to harness the body's T-cell immune system to fight B-cell lymphoma in vivo without having to perform leukapheresis, ex vivo transduction of autologous T cells, and manufacturing of CAR T cells before the lymphoma can actually be treated (typically a 2- to 4-week process). Initial approvals of the CD20/CD3-targeting bispecific antibodies glofitamab[5] and epcoritamab[6] came in 2023 for diffuse large B-cell lymphoma as third-line or higher therapy or for patients ineligible for CD19-targeting CAR T-cell therapy. Mosunetuzumab[7] and odronextamab[8] have also shown success in relapsed/refractory large B-cell lymphoma, but are not yet approved. All these bispecific antibodies can be used more widely geographically but involve repeated injections or infusions, often indefinitely; can still cause cytokine release syndrome and other side effects; and have not yet demonstrated cure potential. To improve the efficacy of bispecific antibodies in large B-cell lymphoma, studies have now been designed to combine bispecifics with novel targeted therapies and/or chemoimmunotherapy,