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CLINICAL TRIALS AND OBSERVATIONS

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Sequencing anti-BCMA therapies in myeloma

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Several therapeutic agents target the B-cell maturation antigen (BCMA) in multiple myeloma (MM). In this issue of *Blood*, Cohen et al address the question of sequencing 2 of these agents in relapsed/refractory MM (RRMM).[1]

Immune therapies are a new avenue in the treatment of MM. The naked anti-CD38 antibodies are already used in frontline therapy after excellent results have been obtained in RRMM.[2]

BCMA, which is expressed on the surface of plasma cells, is another target of immune therapies in MM.[3] Two types of anti-BCMA agents have been developed recently: cellular therapy with chimeric antigen receptor T cells (CAR-T) and 2 therapies incorporating anti-BCMA antibodies (ie, antibody-drug conjugates and T-cell engagers bispecific antibodies (BsAs). At present, several of these 3 types of novel agents are under development and 4 products have been US Food and Drug Administration and European Medicines Agency approved (the antibody-drug conjugate [ADC] belamaf, 2 CAR-T cells ide-cel and cilta-cel, and more recently the bispecific antibody [BsA] Tecvayli).

Until now, these therapies have been most commonly used in heavily pretreated RRMM patients, although many clinical trials are exploring treatment at earlier stages and in combination with other anti-MM agents. Anti-BCMA antibodies have yielded responses in RRMM patients, but in the case of failure or progression after antibody treatment, there are few treatment possibilities. The causes of resistance to anti-BCMA antibodies are not fully known but include defective host immune functions and BCMA antigen escape or loss of expression. Therefore it is important to investigate whether patients who have been exposed to anti-BCMA antibodies can still respond to anti-BCMA CAR-T cells.

In this issue of *Blood*, Cohen et al report the results of a small series of 20 heavily pretreated RRMM patients who previously received anti-BCMA antibodies and were treated with cilta-cel, a BCMA-targeting CAR-T cell. Cilta-cel was selected because in the phase 1b/2 trial Cartitude 1, the rate, depth, and duration of responses in heavily pretreated patients were the best reported for this clinical situation.[4] The current study shows that, after exposure to BCMA-targeted antibodies, either ADC or BsA, cilta-cel therapy is feasible with no new or unexpected toxicity and is quite effective. At a median follow-up of 11 months, 7 of 10 tested patients achieved minimal disease negativity at the threshold of 10 to -5. The overall response rate was 60%, and the median duration of response was 11 months. Overall, these results indicate that using cilta-cel after prior BCMA-targeted therapy may achieve meaningful clinical benefit in some patients. Of note, serum BCMA concentrations decrease after cilta-cel infusion, suggesting an anti-BCMA activity of CAR-T cells. However, 4 patients could not receive the CAR-T infusion (2 deaths and 2 cell collection failures), which argues for sequencing these therapies at earlier stages, pending the results of trials of BCMA-targeted therapies given earlier in the course of disease, including in frontline therapy.

However, considering the cost, access concerns, and toxicities of CAR-T cell therapy, it would be important to determine which patients are most likely to benefit from cilta-cel in this sequence.

Unfortunately, the number of patients in this series is too small and the modalities of previous anti BCMA therapy are too heterogeneous to draw a definitive conclusion. Interestingly, most responders to cilta-cel did not respond to their prior anti-BCMA therapy, suggesting that targeting the same tumor antigen may lead to different results when using cellular immunotherapy vs antibodies. The only predictive factors for clinical response were a shorter duration of exposure to anti-BCMA antibodies (some patients had a short exposure) and a longer interval between the last anti-BCMA treatment and the pre-CAR-T cell apheresis. On the basis of this study, it is not possible to know whether CAR-T cell second therapy might be more active after ADC or after BsA as 13 patients previously received ADC and only 7 received BsA. Therefore more data are needed to better understand the optimal approach to using CAR-T after noncellular anti-BCMA therapy in RRMM. Given that these antibodies will be more readily accessible and are not hampered by the logistic challenges of CAR-T cell production or need for bridging therapy, these data should be forthcoming.

One can envision that, due to current access limitations to CAR-T cell therapy, other BCMA-targeting therapies will be frequently used before CAR-T cells in RRMM. They are off-the-shelf agents and are available to initiate treatment

immediately. However, in centers that have an easier access to CAR-T cell therapy, the sequencing of BCMA-targeting agents may be the opposite.

There are indeed some preliminary experiences with BsA after prior BCMA-targeting agents including CAR-T cells. Results with the BsA teclistamab and erlanatamab are already available. In patients previously exposed to ADC or CAR-T, teclistamab yielded a 52.5% response rate including complete responses with no difference between ADC and CAR-T. The safety profile was similar to that observed in BCMA-naive patients.[5] In the Magnetis MM-3 phase 2 trial of erlanatamab in patients with RRMM, cohort B was specifically focused on prior BCMA-directed ADC or CAR- T. Results from this study are not yet available.[6]

Another possibility for patients previously exposed to BCMA-targeting agents is to use a different target. In the MonumenTAL1 phase 1 trial of the GPRC5D targeting BsA talquetamab, almost 30% of RRMM had received BCMA-targeted therapy.[7] Similarly, cevostamab targeting the Fc receptor homolog 5 showed encouraging preliminary results with responses in 7 of 10 patients with prior BCMA-targeted therapies (ADC or CAR-T).[8]

In conclusion, BCMA-directed therapies represent a major breakthrough in the treatment of RRMM. In addition to a better understanding of the mechanisms of resistance, a crucial question is the optimal sequencing of the different BCMA-targeted therapies. Repeated treatments with these agents appear to be possible, but soon, enhanced benefit and improved outcome may be optimized by their use in better sequencing or at earlier stages.[9]

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

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TORing the impact of sirolimus on immune health

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In this issue of *Blood*, Kumar et al[1] investigate the impact of sirolimus on immune health in a cohort of children treated with sirolimus for multilineage immune cytopenias (m-ICs). Sirolimus, also known as rapamycin, is an antifungal compound first identified in a soil sample obtained from Easter Island (Rapa Nui) as part of a 1960s drug discovery program.[2] Shortly after its isolation, sirolimus was found to be a potent immunosuppressive agent, forming a complex with FK-binding protein-12 that blocks activation of the protein kinase, mammalian target of rapamycin (mTOR), arresting the cell cycle and inducing autophagy.[2] In 1999, sirolimus was approved by the US Food and Drug Administration to prevent solid organ transplant rejection, and over the past 20 years, it has been found to be a well-tolerated drug with an excellent safety profile.[2]

In the early 2000s, sirolimus was studied as a treatment for autoimmune lymphoproliferative syndrome (ALPS), a disorder driven by defects in Fas-mediated apoptosis that causes inappropriate proliferation of $CD4^-$ and $CD8^-$ T lymphocytes, termed "double-negative" T cells (DNTs), resulting in symptoms including lymphadenopathy, splenomegaly, and m-ICs.[3,4] Multiple studies have since confirmed that sirolimus is a highly effective therapy for ALPS, inducing apoptosis of DNTs while promoting the developing of regulatory T cells, leading to the resolution of m-ICs without causing significant immune compromise when used as monotherapy.[5,6] Interestingly, sirolimus has subsequently been shown to be effective in the treatment of m-ICs in patients without ALPS.[7] In many of these patients, sirolimus does not significantly change absolute lymphocyte counts or immunoglobulin levels, and its mechanism of activity remains unclear. However, prior studies of the impact of sirolimus on immune health are not robust.[8]