HAEMATOLOGICAL CANCER

When an embarrassment of riches isn't enough

Krina Patel and Sagar Lonial

Data on a new treatment approach utilizing bispecific monoclonal antibodies targetting B-cell maturation antigen (BCMA) were recently published, yielding very encouraging results in the setting of relapsed and/or refractory multiple myeloma (RRMM). How to safely and effectively deliver this treatment to patients and where it fits in the RRMM treatment paradigm are important questions for the future.

Refers to Moreau, P. Teclistamab in relapsed or refractory multiple myeloma. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2203478 (2022).

Immunotherapies for cancer can promote antitumour immunity through several different mechanisms of action (MOAs), ranging from passively eliciting antitumour immunity with antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) (such as daratumumab, istatuximab, elotuzumab and belantamab mafadotin) to actively enhancing the activity of antitumor T cells via immune-checkpoint inhibition or transduction of chimeric antigen receptors (CARs) against specific tumour-associated antigens (such as idecabtagene vicleucel[1] and ciltacabtagene-autoleucel[2]). Each of these immunotherapy approaches has revolutionized anticancer therapy — nonetheless, for patients with multiple myeloma (MM) several limitations still exist regarding toxicities, access and eventual resistance and disease relapse. Many treatment options are available for MM, although an urgent need for more continues to exist. Therefore, although not soon enough, we now see the emergence of a novel agent with a different immune-based MOA, utilizing a well-known target in MM, B cell maturation antigen (BCMA); this mechanism is T cell redirection or engagement using a bispecific antibody.

T cell redirecting bispecific antibodies or T cell engagers (TCEs) target cancer cells through two single-chain variable fragments: they engage and activate endogenous T cells via CD3 and target these activated T cells to tumour cells through a second tumour-specific antigen. The activated T cells kill the linked cancer cells through cytolysis using granzymes and perforins, which leads to apoptosis. Teclistamab targets CD3 and BCMA expressed on MM cells and is one of the first TCEs evaluated in patients with relapsed and/or refractory multiple myeloma (RRMM). Recently, results of the phase I/II MajesTEC-1 trial demonstrated the overall safety and impressive efficacy of this highly anticipated therapy[3].

Historically, triple-class RRMM, defined as a disease that is refractory to a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 antibody, portends a poor prognosis with overall response rates (ORRs) of approximately 30% and median progression-free survival (PFS) durations of 3–6 months using available therapies[4,5]. A total of 165 patients who received a median of 5 prior lines of therapy (LOTs) were enrolled, of whom 89.7% were refractory to the last LOT, 77% were triple-class refractory (resistant to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody) and 30.3% had penta-drug refractory disease (resistant to bortezomib, carfilzomib, lenalidomide, pomalidomide and an anti-CD38 monoclonal antibody). Other high-risk features such as extramedullary soft-tissue disease and high-risk cytogenetics were seen in 17% and 25.7% of patients, respectively.

Treatment with teclistamab included step-up dosing, to decrease the incidence and severity of immune-related adverse events (AEs) such as cytokine-release syndrome (CRS) and immune effector cell associated neurotoxicity (ICANS). Patients then received the full 1.5 mg/kg dose subcutaneously once weekly at 2–4 days after the second step-up dose. CRS occurred in 72.1% of patients, with the majority being grade 1–2, while neurotoxicities were observed in 14.5%, with 3% having grade 1–2 ICANS. Grade 3–4 cytopenias were common, with neutropenia at 64.2%, anaemia at 44.8% and thrombocytopenia at 21.2%. Infections occurred in 76.4% of patients and were of grades 3–4 in 44.8%, of which pneumonia and COVID-19 both accounted for 12.1% of events.

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At a median follow-up duration of 14.1 months, the ORR at the recommended phase II dose was 63%, with a complete response or better rate (≥CR, including stringent complete response and MRD status) of 39.4%. Median PFS was 11.3 months, duration of response 18.4 months and overall survival (OS) 18.3 months.

The current paradigm of continuous therapy in order to prolong PFS and OS in RRMM necessitates access to newer and more-effective therapies. Given the wealth of ways to target BCMA, how do we place the current data into context? The first question to ask is does the use of one BCMA-directed treatment preclude the use of another? The simple answer, anecdotally, is no. Complete loss of BCMA expression is a relatively rare event, occurring <5% of the time where studied[6,7], and the definition of refractoriness to BCMA-directed therapy is likely dependent upon the mechanisms of action and resistance to each modality (such as CAR T cells, TCEs or ADCs). The next question then is how do we consider sequencing these treatments, and can they be complementary rather than competitive? For patients who need immediate therapy with a novel mechanism of action, off-the-shelf approaches are preferable, thus favouring the use of TCEs or ADCs; however, CAR T cells have the advantage of a

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likely deeper response to a single treatment, which can be attractive for patients, especially in relation to quality of life. To date, a PFS curve plateau has not been observed for patients with RRMM receiving CAR T cells. This lack of long-term remission coupled with the fact that access remains a major challenge for autologous CAR T cells makes sequencing strategies necessary, yet difficult. Potentially, once access and manufacturing are optimized, using TCEs or ADCs as bridging therapies before and/or as consolidation after CAR T cells could lead to improved outcomes and achieve the long-awaited survival curve plateau in patients with RRMM. Finally, infections remain an issue with both CAR T cells and TCEs. Profound plasma cell and B cell suppression using highly effective BCMA-directed therapies will likely lead to increased risks of both typical and unusual infections when considering the use of maintenance or continuous therapy going forwards. Aggressive preventive strategies with appropriate prophylaxis will be needed.

Many unanswered questions remain on how this new class of immunotherapy will fit into the treatment paradigm. The activity and AE profile of teclistamab clearly supports use in patients with RRMM, and despite years of dogma suggesting that T cell activity is poor in this setting, the high ORRs and durability of responses suggest that T cells can be successfully employed using TCEs. In the short term, anticipation for having an agent such as teclistamab as part of the new wave of immunotherapies is high as this will address a major unmet need. With the Prescription Drug User Fee Act date for teclistamab set for August 2022, oncology teams are hard at work creating safe pathways for potential inpatient versus outpatient treatment, which will adequately address the risks of CRS, neurotoxicities and infectious complications. For the future, other TCEs, directed against BCMA[8], FCRH5[9], and GPRC5D[10], are also in later stages of development and might be approved soon. Sequencing and/or combining all of these novel immunotherapeutic agents, especially as they are evaluated in earlier lines of therapy, is exciting, but will need to be conducted in the context of correlative studies that provide guidance on the optimal application of such treatments in the rapidly changing world of myeloma therapeutics.

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1. Munshi, N. C. et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N. Engl. J. Med.* **384**, 705–716 (2021).
2. Berdeja, J. G. et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet* **398**, 314–324 (2021).
3. Moreau, P. et al. Teclistamab in elapsed or refractory multiple myeloma. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2203478 (2022).
4. Lonial, S. et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol.* **21**, 207–222 (2020).
5. Chari, A. et al. Oral selinexor-dexamethasone for triple-class efractory multiple myeloma. *N. Engl. J. Med.* **381**, 727–738 (2019).
6. Samur, M. K. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. *Nat. Commun.* **12**, 868 (2021).
7. Da Vià, M. C. et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. *Nat. Med.* **27**, 616–619 (2021).
8. Lesokhin, A. M. et al. Initial safety results for MagnetisMM-3: a phase 2 trial of elranatamab, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients (pts) with relapsed/refractory (R/R) multiple myeloma (MM). *J. Clin. Oncol.* **16** (suppl.), 8006 (2022).
9. Trudel, S. et al. Cevostamab monotherapy continues to show clinically meaningful activity and anageable safety in patients with heavily pre-treated relapsed/refractory multiple myeloma (RRMM): updated results from an ongoing phase I study. *Blood* **138** (Suppl. 1), 157 (2021).
10. Berdeja, J. G. et al. Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D)×CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM). *J. Clin. Oncol.* **39** (suppl. 15), 8008 (2021).

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