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CAR T cells in multiple myeloma: lessons learned

Vinay Prasad

The question of whether chimeric antigen receptor (CAR) T cell therapies should be used in earlier lines (after 1–2 prior lines of therapy) in patients with relapsed and/or refractory multiple myeloma remains unanswered. Herein, I argue that the use of surrogate end points that lack a robust correlation with overall survival, as well as suboptimal control arms and use of post-progression therapies, limit the ability to make definitive conclusions on the basis of the available data.

On 15 March 2024, the Oncology Drug Advisory Committee (ODAC) of the US FDA considered supplementary marketing authorizations for two chimeric antigen receptor (CAR) T cell therapies used in patients with relapsed and/or refractory multiple myeloma (RRMM)[1]. Both products have previously been approved for patients with RRMM with disease progression after ≥4 lines of therapy and are available commercially. The committee voted 11–0 for ciltacabtagene autoleucel (cilta-cel) and 8–3 for idecabtagene vicleucel (ida-cel) in favour of expanding the use of these products to earlier lines, for patients who have received at least 1–2 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and (at least in one trial) an anti-CD38 antibody. These favourable decisions emerged despite concerns raised by the FDA regarding excess early deaths and limited overall survival (OS) benefits among patients receiving these products[2,3]. Ultimately, CAR T cells remain an important treatment option for patients with RRMM, although patients and physicians should — despite this decision — be made aware that the optimum timing of administration of these products remains uncertain.

Data from two randomized controlled trials (CARTITUDE-4 and KarMMa-3)[2,3] discussed at the ODAC meeting support the use of cilta-cel and ida-cel, respectively, in patients with RRMM. Both assigned patients who had disease that progressed after 1–3 (cilta-cel) or 2–4 (ida-cel) prior lines of therapy to receive the CAR T cell product or investigator's choice of control treatment, chosen from a prespecified set of therapies. Both studies demonstrated clinically and statistically significant improvements in median progression-free survival (PFS) — a composite time to event end point that includes a 50% increase in the serum M-protein as a criterion for disease progression. The ODAC also discussed the immature (cilta-cel) and mature (ida-cel) overall survival (OS) results and concerns about safety. I highlight eight lessons to be learned from this situation.

First, neither trial has demonstrated an OS advantage. With ida-cel, OS analyses were mature and failed to demonstrate benefit, with Kaplan–Meier curves that were ultimately superimposable. With cilta-cel, the curves initially favoured the control arm and later crossed to favour the CAR T cell product. The FDA specifically cautioned that these statistical comparisons of OS results were not prespecified and, therefore, that no statistical testing should be applied and that data are immature. Curves favouring the control arm initially were flagged by the FDA as a sign of increased early mortality from the product and supported by excess deaths, largely owing to disease progression while waiting to receive the product (which is an inherent limitation of the CAR T cell approach).

Second, patients in the control arm of both trials received investigator's choice of therapy, although this choice was restricted to a set of prespecified options. Notably, three highly effective combination therapies (carfilzomib, daratumumab and dexamethasone; carflizomib, isatuximab and dexamethasone; and carfilzomib, pomalidomide and dexamethasone) were not options in both trials, despite being widely used in clinical practice in these specific settings. Limiting the range of 'investigator's choice' of therapies has been described as a potential source of bias that might lead to underperformance of the control arm[4].

Third, the randomized trial evaluating cilta-cel did not permit patients with disease progression in the control arm to receive the CAR T cell product, whereas the trial testing ida-cel did. A representative of the ida-cel trial sponsor argued that OS benefit would have been shown had crossover not occurred[5]. This argument misses the point that failing to find an OS benefit despite crossover shows that earlier treatment is not superior to the current practice of reserving these agents for the fifth line of therapy — precisely the question faced by physicians and patients. Following this logic, prohibiting crossover (a design feature in the cilta-cel trial) constitutes another potential source of bias[6]. When participants in the control arm are deprived of access to potentially beneficial subsequent therapies, a trial cannot answer the question of whether early treatment is superior to current practice. Nonetheless, the ODAC committee members seem to have been impressed that the survival curves appeared visually more favourable in the trial testing cilta-cel, in which crossover was prohibited, and this was reflected in their vote. This decision might send the unfortunate message to sponsors that placing restrictions on access to post-protocol therapy is acceptable in ongoing studies.

Fourth, the resounding votes in favour of both of these products probably reflect oncologists' enthusiasm for these therapies, which have demonstrated high response rates even in patients with cancers that are refractory to multiple prior lines of therapy[7], as well as a growing acceptance that significant improvements in PFS — the primary end point of the trials — is sufficient to change clinical practice, even if such gains are not accompanied by similar improvements in OS. Delaying the time to next treatment is a potential quality-of-life benefit for patients, although receiving CAR T cells can itself be an onerous

process with a substantial risk of toxicities that might offset some of these gains. Ultimately, only longitudinal data on health-related quality of life can adjudicate this question, although these have thus far not been reported.

Fifth, both trials demonstrate the occurrence of concerning and unpredictable toxicities. Drug-induced parkinsonism and neuropathy can be debilitating, and both are idiosyncratic adverse effects of BCMA-directed CAR T cells identified in a small percentage of patients in both studies. Given the small sample sizes, the true incidence of these events is probably unknown. Real-world studies are needed to further clarify the risks of such toxicities.

Sixth, the decision by the FDA to make CAR T cells available to patients with RRMM in earlier lines of therapy will lead many insurers and Medicare to cover this costly procedure. CAR T cell therapy for patients with RRMM carries a formidable price tag of US $370,000–475,000, which does not include any additional costs incurred by medical management of any toxicities (such as cytokine-release syndrome), which have been estimated to swell to a further ≥$50,000 (ref. 8). Certainly, for some patients with rapidly progressive disease, or those concerned about cell harvesting later in the course of disease when their bone marrow is more likely to be hypo-proliferative or exhausted, earlier administration of CAR T cells might be a reasonable approach. Yet, the crossing of the OS curves, and the lack of OS benefit, suggests that delaying the use of CAR T cells is a reasonable approach for most patients. Patients whose cancer is progressing slowly might prefer to defer receiving CAR T cells.

Seventh, both trials started several years ago; therefore, neither is able to assess the role of CAR T cells in the context of the new and rapidly changing therapeutic landscape. The rise of bispecific antibodies directed at the same targets as CAR T cells might provide a preferable off-the-shelf treatment option for many patients. Randomized trials testing whether these agents improve OS are ongoing, and the results are eagerly awaited.

Finally, uncontrolled trials assessing the role of CAR T cells in patients with smouldering myeloma, a precancerous state, are ongoing (NCT05767359). Given the adverse effect profile of CAR T cells, as well as a possible risk of secondary malignancies, the benefit–risk balance of this approach should be reassessed.

Ultimately, in contrast with acute lymphoblastic leukaemia and large B cell lymphoma, CAR T cells are not a curative treatment for RRMM[9]. Although highly effective in generating tumour shrinkage, these therapies have thus far failed to demonstrate convincing improvements in OS in patients with RRMM and come with the risks of increased short-term mortality and idiosyncratic adverse events. Nonetheless, the ODAC remains highly enthusiastic about these products; although their important role in the treatment of RRMM is unquestioned, the optimal sequence of administration of these products remains uncertain, which indicates a need for careful judgment among providers, patients and payers[10].

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Competing interests

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