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Authors
Powell, Kerrington
Russler-Germain, David
Prasad, Vinay

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Idecabtagene vicleucel: questions regarding the appropriate role and cost

Idecabtagene vicleucel (ide-cel, Abecma, Bristol Myers Squibb [BMS], New York, NY, USA), is the first FDA-approved cell-based gene therapy for multiple myeloma, the first chimaeric antigen receptor (CAR) T cell therapy directed at B-cell maturation antigen (BCMA), and a drug with an astonishing price tag.[1] BMS and Bluebird Bio, marketing in unison, have listed the CAR T-cell therapy at a price of $419 500 per treatment.[2] Approval was based in part on the KarMMa study (NCT03361748), a phase 2 trial that found a 73% response rate and a median progression-free survival of 8·8 months based on a modified intention-to-treat analysis.[3] This recent approval serves as an opportunity to assess ide-cel's clinical implications and explore whether this price tag is sustainable for a therapy that does not appear to cure even a fraction of patients.

While other CAR-T therapies are similarly priced, this is the first approved CAR-T that, despite impressive objective responses and induced remissions in even refractory cases, is non-curative.[4] Not only is the cost high, but the budgetary impact may be massive given the large number of eligible multiple myeloma patients who are on Medicare.[5] Whether and to what degree the cost of ide-cel is sustainable for a therapy that will only delay inevitable progression is a matter of debate. That said, the budgetary impact and emerging insurance conflict pose the question, how willing is society to pay for a toxic therapy that patients will eventually progress on? And if so, is there any value in a pricing schema that reimburses parties proportionate to a patient's duration of response?

To understand the specific case of ide-cel, price is not the only toxicity that must be accounted for. In the KarMMa trial, grade 1 and 2 cytokine release syndrome (CRS), the most prominent toxicity of CAR-0T therapies, occurred in 107 patients (84%), with five patients (4%) and one patient (<1%) experiencing grade 3 and 4 CRS respectively.[3] Ide-cel incorporates a 4-1BB costimulatory domain, which tends to have CRS onset later and with less severity than the CD28 varieties.[6] However, interpretation of CRS events in a clinical trial and forecasting of real-world tolerability greatly depends on understanding the specific CRS grading criteria used in the study (e.g., Lee *et al.*).[7] Clarifying this context is imperative to determine whether or not there is realistic potential for ide-cel administration in the outpatient setting. With 30% of patients experiencing grade 2 CRS (i.e. symptoms require or respond to fluids or low-dose pressors), the likelihood of outpatient use falls considerably.

Why are patients destined to progress on a modality with high response rates? One explanation may be that minimal residual disease (MRD) status fails to identify residual disease just beyond the threshold of detection. Among patients, 26% achieved MRD-negative status in the KarMMa trial, yet the median duration of response was 10·7 months, and there is no evidence of a fraction of patients with indefinite, durable remission. The trial then highlights limitations of MRD, both to identify cured patients, and as a regulatory end-point (e.g. different measurement techniques combined with variable sensitivities/cut-offs). The ability of a novel drug coming to market to push tumour volume below an MRD cut-off is only valuable insofar as doing so achieves a cure in a subset of MRD-negative patients, and/or patients achieve longer overall survival durations thanks to deeper remissions. However, while there is little debate that MRD serves as a prognostic marker (i.e. if a patient is MRD-negative, a longer duration of survival is expected than otherwise), this association does not prove that MRD is a valid surrogate end-point. In order to prove that MRD is a surrogate suitable for regulatory decision making, one would ask whether therapies that increase MRD rates also increase survival across randomized trials that measure both end-points. To date, that analysis has not been performed, in part because older trials, which might be leveraged to answer this question, did not routinely perform MRD analysis.

As the number of CAR-0T immunotherapies continues to increase, so do the proclamations of improvement in quality of life (QoL) during treatment-free intervals.[4,8] There is value in QoL benefits, but what price and upfront toxicity profile a patient is willing to tolerate is very much in the eye of the beholder. Discounting toxicity, a $419 500 price tag is still a hefty cost for an 11-month treatment-free interval, considering that a prorated triplet regimen in this context may cost less. This translates into a roughly $40 000 cost per month of delayed progression, which exceeds the price of other novel salvage myeloma drugs. The high cost can begin to be rationalized when entertaining concepts such as outcomes-based contracts, which Novartis offered with their development of the CAR-0T therapy, tisagenlecleucel (Kymriah). These contracts offer no charge if patients fail to respond in one month, but also come with a wealth of criticism such as an arbitrary cut-off point, ethical concerns, and excessive $475 000 price tag.[9]

Irrespective of cost, the most alarming concern of ide-cel is its potential role in the clinical setting. Since this treatment

is likely non-curative, physicians may anticipate an eventual relapse and justify maintenance therapy with active but expensive agents such lenalidomide, carfilzomib, bortezomib, or daratumumab. The treatment-free interval and theoretical accompanying QoL gain anticipated for patients responding to ide-cel per the KarMMa study protocol would then vanish, with patients unable to escape the burden of therapy-related toxicities (both medical and financial).

In conclusion, it is crucial to question whether non-curative therapies like ide-cel are worth it. The drug clearly generates response in some patients who have progressed on many therapies, and ongoing randomized trials of this agent *versus* doublet or triplet regimens will clarify its role. At the same time, we must ask that the cost of therapies be proportionate with their benefits. For a drug that is non-curative, we must ask ourselves if the price tag accurately reflects ide-cel's ability to transform lives, especially if ide-cel's clinical value substantially declines upon administration of subsequent maintenance therapies. Ide-cel pushes us to new firsts — the first BCMA CAR-T therapy, and the first non-curative CAR-T. The implications for health care systems require careful consideration.

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Author contributions

VP and DRG conceptualized the study design; KP reviewed literature; VP and DRG reviewed and confirmed abstracted data; KP wrote the first draft of the manuscript; and all authors reviewed and revised the subsequent and finalized draft of the manuscript.

Conflicts of interest

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Kerrington Powell[1]
David Russler-Germain[2]
Vinay Prasad[3]
[1]College of Medicine, Texas A&M Health Science Center, College Station, TX, [2]Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO and [3]University of California San Francisco, San Francisco, CA, USA.
E-mail: vinayak.prasad@ucsf.edu

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