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CASE AND COMMENTARY

How Should We Determine the Value of CAR T-Cell Therapy?

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Abstract

In 2017, the US Food and Drug Administration approved the first chimeric antigen receptor (CAR) T-cell therapies for patients with relapsed or refractory B-cell leukemia and selected B-cell lymphomas. This novel form of cellular immunotherapy creates a "living drug" that effectively reprograms a patient's T cells to target specific antigens on the surface of a tumor. The therapy has high response rates in patients with refractory disease, although a single infusion of CAR T cells costs hundreds of thousands of dollars. A value analysis is required to determine whether and how to offer patients these expensive, customized drugs.

Case

The US Food and Drug Administration (FDA) approved the first chimeric antigen receptor (CAR) T-cell therapy in 2017 for patients with relapsed or refractory B-cell malignancies. This novel form of cancer immunotherapy uses a patient's own T cells to customize a drug to treat that particular patient's B-cell malignancy. According to then-FDA Commissioner Scott Gottlieb, this development "marks another milestone in the development of a whole new scientific paradigm for the treatment of serious diseases."[1]

One course of this precision treatment costs $373 000 or $475 000 (depending on the type of B-cell malignancy),[2,3] with high 1-year survival rates in clinical trials (at least 41%, depending on type of B-cell malignancy).[2] The high costs of CAR T-cell therapy are not unique in the rapidly expanding world of cancer drugs. Using analytical tools, economic principles, and the behavioral psychology of decision science, payers and health care organizations need to do a value analysis to determine whether and how to offer patients these expensive, customized drugs. Such an analysis is necessary to inform policy and practice decisions about potential risks and benefits of making these drugs available for some patients' needs relative to those of other patients.

Commentary

B-cell acute lymphocytic leukemia (B-ALL) is the most common cancer of childhood.[4] For most patients, prognosis is good, with 5-year overall survival reaching 90%.[5] However, for patients who do not achieve remission or experience relapse and require second- and

third-line therapies, prognosis is poor.[2,6,7] The FDA has now approved the use of 2 novel CAR T-cell therapies to treat B-ALL and diffuse large B-cell lymphoma (DLBCL). In August 2017, the FDA approved tisagenlecleucel, an anti-CD19 CAR T-cell therapy, for use in patients (through age 25) with B-ALL.[8] In October 2017, axicabtagene ciloleucel was the first CAR T-cell therapy approved by the FDA for use in relapsed or refractory DLBCL.[1] In 2018, tisagenlecleucel also received FDA approval for use in relapsed or refractory DLBCL.[9] These innovative therapies involve genetic reprogramming of a patient's immune surveillance cells (T cells) and hold great promise for treating these and other malignancies.

Nevertheless, these therapies are expensive, with the 2 approved drugs priced at $475 000 for B-ALL and $373 000 for DLBCL.[2,3] With limited data on long-term survival, questions about the cost effectiveness and value of these drugs are worth asking.[2,3] In what follows, we examine whether and how to offer patients CAR T-cell therapy. More specifically, we address (1) value analysis and its application to CAR T-cell therapy, by means of which payers and health care organizations assess whether to offer patients these drugs in light of their expense and the risk of adverse effects on other patients and resources; (2) factors that might complicate equitable access to these drugs; and (3) how much patients and families should be told about these therapies' costs.

Measuring Value

As medicine advances, costs of care tend to rise. In a health system with finite resources, decisions must be made about how to allocate funds, justly distribute risks and benefits of innovations, and assess and interpret new interventions' value. The principle of distributive justice suggests that health care resources should be fairly and equitably allocated. In order to be useful for resource allocation decisions, value-based approaches to care must not only be evidence based but also incorporate quality-of-life considerations and costs.[10] Value is commonly measured via cost effective analysis using measures such as life years (LY), quality-adjusted life years (QALY), and associated incremental cost effectiveness ratios (the net cost divided by the net QALYs gained) that enable comparison of interventions in terms of their value. These measures facilitate a clearer understanding of how to maximize efficiency by quantifying how to spend the least amount for the greatest gain.

The Institute for Clinical and Economic Review (ICER) "evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs."[2] In 2018, ICER analyzed CAR T-cell therapies, comparing their clinical effectiveness (remission rates, event-free survival, adverse events) with that of comparable treatment regimens using projective cost effectiveness models.[2] For B-ALL, the total cost of therapy was $667 000 with 10.34 LYs and 9.28 QALYs gained. For a comparable chemotherapy (clofarabine based), the total cost of therapy was $337 000 with 2.43 LYs and 2.10 QALYs gained. In the model

evaluating axicabtagene ciloleucel for DLBCL, the total cost of therapy was $617 000 with gains of 7.35 LYs and 5.87 QALYs. For the comparable chemotherapy, the total cost of therapy was $155 000 with gains of 3.23 LYs and 2.48 QALYs. Despite the higher cost of the CAR T-cell therapy in both groups, gains in life years and QALYs were also greater in both groups. As a result, the incremental cost effectiveness ratios were $46 000 per QALY gained for CAR T-cell therapy compared to chemotherapy in B-ALL and $136 000 per QALY gained for CAR T-cell therapy compared to chemotherapy in DLBCL.[2]

Integrating Equity Into Value Analyses

Decision science involves a multimodal analysis of the economic, political, societal, and ethical implications associated with the outcome of a decision.[11] While cost effectiveness measures yield numbers that can be used to define and compare value, we must also consider equity in health care resource allocation decisions.[12] Once QALYs and incremental cost effectiveness ratios have been generated, we must then determine threshold(s) for acceptable value. In the United States, thresholds of $100 000 or 150 000 per QALY gained have been suggested as a reasonable upper bound for an intervention to be deemed cost effective.[13] Others, however, argue that what counts as an acceptable threshold is arbitrary and does not necessarily facilitate just resource distribution.[14] In addition, because we are operating under a fundamentally flawed model of how drug prices are set, QALY calculations can in some circumstances not only determine what is cost effective but also how drug manufacturers artificially inflate prices.

Although ICER's cost effectiveness analysis would suggest that CAR T-cell therapy is of value, comparative value does not equate with equity. It does not consider issues of just allocation—including access to therapy—and individual and institutional bias. Furthermore, given limited short-term outcomes data, it becomes difficult to justify the use of CAR T-cell therapy over alternative therapy options. It is similarly difficult to expect insurers to cover a one-time intervention costing close to fivefold the US gross domestic product per capita.[15] But a purely utilitarian calculus is not appropriate, either. If the goal were to simply maximize health benefit, the majority of funding for cancer treatment would be funneled to improving malaria treatment and water quality in the developing world. We, as a nation and as a society, are comfortable absorbing disproportionate costs, but where the line between acceptable and unacceptable costs should be drawn is much more complicated.

Other Factors and Implications

Despite the promise that CAR T-cell therapy holds, it might be too soon to understand its true value. As discussed, although initial outcome projections show favorable cost effectiveness, questions remain with respect to whether there is equitable and just access to therapy. Let us consider complicating issues of age, insurance coverage,

clinician bias, and disease status, and the effects that these factors might have on just or equitable access to CAR T-cell therapy.

1. The definitive licensing trials of tisagenlecleucel started at age 3 years,[16] yet the drug has been approved for children ages 0 to 25 years.[8] Is it appropriate to offer and reimburse a therapy for infants or toddlers when efficacy data is limited in this age group? Likewise, should it be offered and reimbursed for young adults with B-ALL over the age of 25?

2. The Centers for Medicare and Medicaid Services recently proposed coverage for CAR T-cell therapy in an approved study registry.[17] While this policy change will expand access to therapy to those covered by Medicare, what does it mean for patients on Medicaid, and how will other insurers respond? How might differing coverage models influence which therapy clinicians choose to offer or what therapy patients are able to choose?

3. The drug manufacturer of tisagenlecleucel has created an outcomes-based agreement that only requires payment for those patients showing morphologic regression within one month of CAR T-cell infusion.[3] This begs the question of whether such a payment model could incentivize physicians to use this product. While payment for the drug will occur regardless of outcome, if the company selling the drug takes on the cost (and presumably passes it on to consumers), might that simplify reimbursement and make it a more enticing product to use? If so, it would seem that stakeholders need to be privy to such potential for bias.

4. Not all CAR T-cell recipients are expected to respond the same way. Patients with a higher disease burden have a greater likelihood of developing toxicities following CAR T-cell infusion.[18] Many patients might require an allogeneic bone marrow transplant as consolidative therapy post CAR T cells.[19] These complications could significantly reduce the predicted value of the therapy given its high cost and negative effects on quality of life, raising questions about whether we should be offering CAR T-cell therapy to patients we expect will have worse side effects or require additional intensive therapy.

Patient Involvement and Ethical Implications

As we consider issues of value and equity, we must also assess the degree to which patients should be involved in the decision-making process regarding the use of expensive therapies. In some situations, some or all costs of considered interventions fall to patients, making cost a major factor in patient decision making. A 2009 statement by the American Society of Clinical Oncology "affirms the critical role of oncologists in addressing cost of care with their patients.... [C]ommunication with patients about the cost of care is a key component of high-quality care."[20] Financial toxicity is indeed a

major and understudied barrier to medical treatment in the United States and suggests the importance of the question of whether costs should be included in CAR T-cell therapy discussions with patients.

Arguments can be made for limiting patient involvement. Opponents to the notion that cost should be discussed with patients could argue that the majority of costs are not incurred by most patients. Some might argue that disclosure of cost could be interpreted as pressure not to pursue CAR T-cell therapy or that discussion of cost might overwhelm patients already facing difficult situations.

Yet others still might argue that cost information is relevant to patient decision making. Some patients have their own views on public health and resource allocation. Others might find comfort in knowing the amount being spent to try to save their life. For many patients, any cost is a financial toxicity, and having the numbers will factor into their treatment decision even if co-pays are a fraction of total expense. In the case of CAR T-cell therapy, some of the costs are hidden or delayed, as the cost of T cells accounts only for T-cell retrieval, modification, and infusion—not for hospitalization, subsequent therapy, or the inherent complications of cancer treatment, both expected and unexpected.[3]

Regardless of the merits of these arguments, we must consider that withholding cost information from patients could be unjust. Should not all patients be offered all relevant information, including cost, that could influence their health care choices? Moreover, should they not be offered cost information in a form they can understand? Another key and often overlooked component in disclosure is information evaluability, which requires including "use-relevant contextual information."[21] More specifically, price per QALY has no immediate relevance to patients who care most about what they will need to pay out of pocket. It certainly does not relate to how expenses incurred by society at large might influence others. How to efficiently or clearly integrate cost and equity into a decision aid or other discrete-choice tool remains a fundamentally unresolved question.

Conclusion

Decisions about allocation of health care resources require a multimodal approach. While the numbers suggest that there might be great value in CAR T-cell therapy in B-ALL and DLBCL with regard to cost effectiveness, measures of value with regard to equity are less clear. Until access to these therapies expands and more data accrue, we must temper our excitement about CAR T-cell therapies with the reality of their multifaceted impact on our patients, their families, and the health system as a whole.

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