Chimeric antigen receptor T cells, a savior with a high price

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Abstract: Chimeric antigen receptor (CAR) T cells represent a medical and scientific breakthrough that may represent a paradigm for the future of personalized medicine in the age of cancer immunotherapy. As with many new cancer agents, such novel and incredible results come with a high price. At the time of the writing of this article, there are two CAR T cells available, Kymriah, produced by Novrtis with a price tag of US$475,000 and Yescarta produced by Gilead Pharmaceuticals with a price tag of US$373,000, neither price including the required hospital admission in order to administer the agent in addition to potential treatment of side effects. There are several issues that are imperative to recognize when understanding the high cost, however the two more pertinent issues are low availability of the agent and no billing code. While only approved for less than a year, there are thoughts about how to bring the price down with more approved CAR T cells and more center with the ability to administer this therapy, however results may be years away before they are realized. In the short term, insurance companies are grappling over how to pay for CAR T therapy, with one of the biggest voids concerning the absence of a billing code for CAR T cells. Regardless, its high price tag highlights moral issues underlying value-based payments and whether the treatment is worth the cost while evaluating the juxtaposition of life years and monetary values. As CAR T cells expand the boundaries of immunotherapy with extraordinary results, the need for a lower price in combination for more availability of CAR T cells will grow until some of these fundamental issues are addressed.

Keywords: CAR T cells; quality-adjust life years (QALY); medicare; immunotherapy; global oncology

Submitted Feb 09, 2018. Accepted for publication Apr 02, 2018.
doi: 10.21037/cco.2018.04.02
View this article at: http://dx.doi.org/10.21037/cco.2018.04.02

Seven years ago, a 7-year-old girl from a Philadelphia suburb, Emily Whitehead, received a new type of cancer treatment called CAR T cells at the University of Pennsylvania. Today she is fourteen years old and disease free, but CAR T cells, despite being an active and approved treatment, is not yet in widespread use. In this article we will discuss why that is so.

Chimeric antigen receptor (CAR) T cells, immune system cells extracted from a patient, engineered ex-vivo to fight cancer cells, and then reinfused into the same patient; represent an exciting immunotherapy that first gained worldwide attention in a 2012 New York Times article titled "*In Girls Last Hope, Altered Immune Cells Beat Leukemia*." In 2012, Dr. Carl June led a team that created and infused CAR T cells at the University of Pennsylvania's Hospital system.

Since August 2017, there are two approved CAR T drugs available in the United States: Kymriah, which is produced by Novartis, and Yescarta, produced by Gilead Pharmaceuticals. Kymriah has a listed price of US$475,000 and Yescarta has a listed price of US$373,000. Not included, but adding to costs overall, are those of a lengthy hospital stay, outpatient follow-up and supportive care for the prevention and treatment of complications, expected to amount to more than US$547,000, possibly leading total expenses to exceed US$ 1 million per patient. Costs could increase further with the well-described and feared complication known as cytokine release storm, where large quantities of interleukins and cytokines are released causing dangerously high fevers, neurotoxicity, and coma.

Due to the complexities associated with treatment, only 15 hospitals in the United States have authorization to

administer CAR T Cells. As such, until the fall of 2017, only a handful of patients has received Gilead Sciences Inc.'s Yescarta. Not surprisingly, as outlined in the costs above, the biggest barrier is payment. There are currently no billing codes for CAR T cell treatment and delays in payment have put hospitals in a precarious conundrum, as they have to choose between optimal and opportune patient treatment versus the risk of not being reimbursed and therefore going out of business. In addition, it has been noted that about half of the patients who receive CAR T cells would be covered by Medicare, which has stringent guidelines in place before approval. As of January 2018, the absence of a billing code (specifically a J-code) for the potentially lifesaving therapy continues to be a barrier for approved cancer centers to prescribe CAR T cells. Despite FDA approval, Medicare still has to meet and determine its coding terminology for the therapy. Unfortunately updates to billing codes only occur once a year and will not be reviewing CAR-T cells until spring 2018. For many, this will prove to be too long a wait as patients who need CAR T cells are advanced in their disease course and need treatment as soon as possible. On the other end of the spectrum, private insurance companies, including, but not limited to Anthem Inc has been evaluating on a case-by-case basis.

Regardless on how the costs will be covered, the derivation of the cost of CAR T cells is something that is not an exact science. Research and development (R&D) costs have been somewhat elusive and the public is compelled have faith in numbers and a process that are not easily accessible to the public. At any rate, the public funding contributes a significant portion for the drug and in the end, the actual payment for the drug itself constitutes the other portion. To complicate things further, money allocation in R&D is pushed towards areas that create the most revenue. In the case of CAR T cells, this is good in the sense that an effective drug is constantly evolving for better results, however, its high costs still make it prohibitive for patients who need it. In essence, there is not much transparency in an area that calls for it more than ever considering the high cost high reward profile of CAR T agents.

On a global scale, would more availability of an agent decrease the price of a drug? Certainly this would go along with simple economics that increasing the amount of a product would bring down cost. Unfortunately, in medicine, this is not always true. The quality of the drug may not be matched with that found in the companies mentioned above. In addition, this could take years before commercially available and possibly vetted. In addition, a different drug may have different side effects that could increase the cost of the drug if used out of the United States, especially if hospital stays are required. Regardless, investigators in other countries are attempting to develop similar technology without infringing current patents, but only time will tell if these lead to regulatory approval and availability of CAR-T outside the United States.

Given the delay with CAR T cells approval and then repayment, the issue of timing comes into play. CAR T cells are for relapsed/refractory disease. Given these characteristics, some patients may be clinically stable to wait long enough for approval, but quickly decompensate while awaiting approval. The turnaround time of 2 weeks it takes to collect the cells, engineer them, and then infuse them back to the patient compounds the problem. As it currently stands, the logistics of giving CAR T cells rely on the patient being sick enough to be eligible for therapy, but not sick enough to preclude them from treatment. Many patients in this category are on waiting lists at a variety of different centers, awaiting insurance approval. Interestingly, despite the cost, there are patients at MD Anderson, for example, who have signed waivers, confirming their intention to pay the cost of the treatment if insurance does not cover the costs as reported by Medscape in January 2018. This, of course, brings up an interesting question, how much is too much for the cost of life? More pertinent, what is the optimal extension of life with an appropriate price? In addition, it may be easier to sell to the public an expensive therapy that will extend the life of a child, but what about for those patients of advanced age?

In addition to an exercise in economic and financial processes, the cost of CAR T cells also raises a significant moral issue and further highlights the importance of discussing value-based payments, and whether the treatment is otherwise worth its cost; ultimately creating outcry from patients and physicians. Other high costs medications, such as Sovaldi for hepatitis C, have come under criticism in the past for a high price tag; however, expensive treatments that are highly effective can be cost effective. This 12-week treatment course, while priced at US$84,000 is considered to cut down total costs of long term treatment of chronic hepatitis C, as reported by the spokesperson for Sovaldi's manufacturer, Gilead, published by the Washington Post in 2015. Other new treatments for hepatitis C fit this bill, and emerging data suggest this may also be the case for CAR T cells, at least in the United States. Both treatments intend to

generate long-term efficacy without ongoing and indefinite therapy, such as chemotherapy and targeted agents for metastatic disease.

Another interesting proposal revolves around an outcomes-based approach. In this model, patients would only incur a charge if there were a response. Novartis has exercised this concept with their heart failure agent Entresto (reported by Reuters in February 2016, and Merck with its diabetes drugs Januvia and Janumet (reported by Reuters April 2009). In Europe, a graduated payment system has been proposed in a way that the government will pay amounts at the end of additional years of life the patient benefits from. This perhaps highlights an important concept of quality-adjust life years (QALY), a concept that placed a price on years of life and years of worth and possible extra cost. On the other hand, there is evidence that despite these upfront costs, CAR T cells offer a chance for cure versus chemotherapy that may include monthly treatments for extended periods. CAR T cells may provoke a phenomenon otherwise known as T cell education, where cytokines and other signaling pathways may instruct recipient T cells on how to kill malignant cells.

Outside of moral issue juxtaposing life years and monetary values, physicians may not completely understand the cost of the therapy nor how this should influence a decision. One may raise the question whether it really is the physician's job to know these costs. While the argument may be that physicians should only deal with medical issues, there may not be a better time to argue the contrary as stated by Mitesh Patel, professor of medicine and health care management at the University of Pennsylvania, addressing salient points in an August 2016 interview. The US is among the top most expensive countries for medical care and among the worst in health care efficiency. One of the major contributors to this unfortunate statistic is wasteful practice, including unnecessary treatments and overpriced drugs. CAR T cells represent a slightly different and upfront situation where physician awareness of cost of treatment is unavoidable, given its incredible efficacy and limited versions available. This would differ from other frequently prescribed medications, such as insulin, which has gone from being affordable to becoming too expensive for many, as prices have risen dramatically over time. This introduces the argument immediately as physicians will bear the burden of figuring out what patients can afford to do as opposed to what patients need.

Regardless, the issue of CAR T cell reimbursement and payments need to be solved; as there are over 120 CAR T-cell based therapy trials for cancer and other conditions such as autoimmune diseases as seen on clinicaltrials.gov. With the advent of immunomodulating agents such as PD-1, PD-L1, and CTLA-4 agents, unleashing the immune system's ability to treat cancer is here to stay. Making this agent readily available will be the hardest task and as trials progress, CAR T cells in combination with other immune modulators will further be explored. The United States has historically been behind in cost effective healthcare in the past, but given this new and groundbreaking therapy, this may represent an opportunity for the United States to create a payment paradigm that could be emulated throughout the world.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Cite this article as: de Lima Lopes G, Nahas GR. Chimeric antigen receptor T cells, a savior with a high price. Chin Clin Oncol 2018;7(2):21. doi: 10.21037/cco.2018.04.02