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Editorial

The Future of Chimeric Antigen Receptor T Cell Therapy for the Treatment of Multiple Myeloma

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On June 29, 2007, the first iPhone was released in the United States, and there was a feeling it would be an extraordinary, life-changing product. The iPhone revolutionized how we interact with phones, more specifically, smartphones, which now serve as an extension of our lives in what essentially amounts to an obligate symbiotic relationship. This product, called the iPhone 2G, was only the first iteration of many subsequent generations of iPhones, and came at a then-hefty price of $599 for the 8-GB model. The development of chimeric antigen receptor (CAR) T cell therapy for multiple myeloma (MM) and other malignancies is in many ways analogous to technological advancement represented by the iPhone. Although CAR T cell products for MM are currently in their infancy, there is much enthusiasm and hope for this treatment modality [1].

The adoptive transfer of genetically modified T cells to recognize malignancy-associated CD19 has led to the approval of 2 products on the basis of pivotal phase II studies: tisagenlecleucel (Kymriah) for B cell precursor acute lymphoblastic leukemia in children and young adults and diffuse large B cell lymphoma (DLBCL), and axicabtagene ciloleucel (Yescarta) for DLBCL [2,3]. CAR development in B cell malignancies has served as a roadmap for their development in MM, particularly for use in conditioning chemotherapy and managing cytokine release syndrome (CRS) and neurotoxicity [4]. The first generations of CAR T cell therapy for MM have focused on targeting B cell maturation antigen (BCMA). BCMA is expressed with varying intensity on the surface of plasma cells [5]. Data are available from 4 different phase I trials targeting BCMA.

The National Cancer Institute used a CD28 costimulatory domain and reported data from 26 patients. At the highest CAR T cell dose level of 9.0×10^6 cells/kg, 13 of 16 patients (81%) had a hematologic response [6]. The University of Pennsylvania incorporated a 4-1BB costimulatory domain and have reported data from 24 patients enrolled into 3 cohorts of differing CAR T cell doses with and without cyclophosphamide conditioning. In the higher-dose cohort (1 to 5×10^8 CAR T cells/kg) with cyclophosphamide conditioning, 6 of 10 patients (60%) experienced a hematologic response [7]. Bluebird bio has reported data from 43 patients from a bb2121 construct with the 4-1BB costimulatory domain. A hematologic response occurred in 29 of 36 (81%) patients who received a CAR T cell dose $\geq 150 \times 10^6$ cells/kg, with a prolonged duration of response in most patients [8,9]. Finally, Nanjing Legend Biotech reported on 19 patients given a median CAR T cell dose of 4.7×10^6 cells/kg, using a CAR known as LCAR-B38M, which binds BCMA at 2 distinct epitopes with an unspecified costimulatory domain. In this trial, 19 of 19 patients (100%) experienced a hematologic response [10].

At this point, the future of CAR T cell development includes several important certainties and uncertainties. It is certain that these initial studies will continue to progress forward, including the bb2121 construct, which is currently being evaluated in a phase II registration trial (ClinicalTrials.gov; NCT03361748) and challenging established triplet regimens in earlier lines of therapy in a randomized study (NCT03651128). CAR T cell products targeting various antigens are currently being developed and tested, including other BCMA constructs (NCT03318861, NCT03338972, NCT03430011, and NCT03288493) [11], kappa light chain [12], CD38 (NCT03464916), and CD19 [13]. Many others are in earlier phases of development [14]. CARs will be tested extensively in nearly every phase of MM management.

Just as the iPhones have become increasingly more sophisticated with subsequent generations, so will CAR T cell technology. Advancements being studied include the rapamycin-induced caspase 9 suicide gene (rapaCasp9) to enable inactivation of CAR T cells in the event of excessive toxicity [15]. Genomic editing of preexisting T cell receptors with CRISPR-associated protein-9 (Cas9) technology is being evaluated to enhance expression of

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the T cell receptor in target cells, leading to more effective malignant cell death [16]. Development of programmable T cell responses with the synNotch receptor is being researched to permit the use of custom therapeutic antibody payload, cytokine secretion, and T cell differentiation [17]. Other technologies in development include the use of zinc finger nuclease gene editing to develop allogenic CAR T cells and the use of polymeric nanoparticles to modify circulating T cells in vivo to express tumor-specific CARs [18,19]. High-dose melphalan followed by infusion of autologous hematopoietic cell transplantation (auto-HCT) has served as a highly effective treatment for MM. It is feasible that auto-HCT could serve as a platform in combination with CAR T cell therapy to incorporate the principles of disease debulking while inducing deep lymphodepletion with immunotherapy. Research evaluating auto-HCT in combination with CD19 CAR T cell therapy is early in development [20].

Although the enthusiasm surrounding CAR T cell therapy is second to none, several questions remain as this strategy faces some challenges not shared by any previously studied approach to MM treatment. Can the optimal dose for disease control be achieved without overwhelming CRS and neurotoxicity? Is the persistence of viable CAR T cells necessary or feasible? Given that most patients who respond and obtain eradication of minimal residual disease (MRD) from the marrow environment still eventually relapse [8], can CAR T cells reach malignant plasma cells effectively in extramedullary sites? Is the persistence of CAR T cells necessary for long-term disease control?

Along with these scientific questions are other, more practical questions. Can this technology be scaled up to become a mainstream therapy for a disease that affects nearly 30 000 Americans each year? If so, can we train the workforce and develop the facilities to deliver such therapy to a large number of patients?

It has been long known that MM is susceptible to immune therapies, as evidenced by allogeneic hematopoietic cell transplantation (allo-HCT) [21–23]. Allo-HCT offers a small but definitive curative potential; however, this is complicated by a high rate of nonrelapse mortality, which adversely impacts overall survival [24]. In the bb2121 study, the median progression-free survival in patients achieving MRD-negative status was 17.7 months [8,9]. In addition, the duration of complete response was as not long as is seen with other therapies.

There are several possible explanations for this. One is that complete response with other therapies is seen mostly in earlier lines of therapy. CAR T cell therapy has been used in the most heavily pretreated patients, where the kinetics of growth of subdetection in MM cells may be a lot faster. Another explanation may be related to a biological difference in the mechanism by which CAR T cell therapy induces response by requiring ongoing CAR T cell suppression of the MM clone for disease control. In this case, recurrence may be facilitated by a diminishing CAR T cell population. This problem may be overcome with redosing or combination therapy. Finally, it is possible that patients with heavily pretreated disease are more likely to have disease in sites that are not sampled by MRD testing and are less assessible to CAR T cells (eg, extramedullary disease).

The current success of CAR T cell therapy lies in the eye of the beholder. A median progression-free survival of 17.7 months in heavily pretreated patients with MM with no meaningful available treatment options is a considerable advancement. However, in cases with anticipation of cure, the initial results may be disappointing. How CAR T cells are currently being used can result in suboptimal response, development of resistance, and eventual relapse. However, long-term follow-up of these early studies is needed to fully understand the potential duration of remission after CAR T cell therapy. It is possible that, as with allo-HCT, a small subset of patients may have benefited from extended remission and possible cure.

There is hope that when CAR T cell therapy is used at therapeutic doses and perhaps earlier in the course of treatment or with more sophisticated technological advancements as mentioned above, this may lead to the Holy Grail of cellular therapy-mediated destruction of all residual clonal plasma cell disease with subsequent cure.

The most recent iPhone XS Max is priced at $1099. As CAR T cell therapy develops, so will the costs of development and implementation increase. How this will affect the routine use of this promising technology in routine clinical practice is unclear. The cost of tisagenlecleucel and axicabtagene ciloleucel for treating lymphoma is approximately $373,000, and the cost of tisagenlecleucel for treating leukemia is $475,000. The total cost of these agents is even higher when hospitalizations and management of complications, such as CRS, are included [25]. Financing and reimbursement of these costs from the Centers of Medicare and Medicaid Services likely will be limited to centers of excellence to limit complications and mitigate costs and will also require patient-reported outcome measures. Current CAR T cell production occurs ex vivo, and one approach to eventually overcoming the high manufacturing cost involves in vivo technology, as mentioned above [19].

In summary, CAR T cell therapy for treating MM offers an innovative management approach with early indicators of success based on multiple phase I trials. The future of CARs includes novel antigenic targets and more sophisticated constructs tested in all phases of MM management. Methods to mitigate costs to allow for routine implementation will be important.

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