Molecular Therapy
Editorial

Next Steps in the CAR Journey of a Thousand Miles

The US Food and Drug Administration's (FDA's) recent approval of Kymriah (tisagenlecleucel) for the treatment of acute lymphoblastic leukemia[1] represents a triumph for the academic and pharmaceutical industry collaborators who enabled the success of this CD19 antigen-directed chimeric antigen receptor (CAR) T cell product. The stunning complete response rate in otherwise refractory disease has rightly attracted enormous attention and comment,[2] which will not be added to here. Of almost equal importance, however, is that approval is focusing attention on the new resources and policies required if the success of CD19 CAR T cell treatment of B cell malignancies is to be more broadly replicated. Otherwise approval of CD19 CAR T cells will be a "man-on-the moon" event in the immuno-oncology space that, as in the original space program, will be followed by decades of more limited and less newsworthy accomplishments.

If T cells are instead to become a major component of cancer immunotherapy for all human malignancies, we will need to change our research and development processes, patient care practices, and integration of health economics into early-phase drug development.

The approval of tisagenlecleucel came after more than 20 years of basic and developmental research by academic and industry investigators.[3] A broader reach for T cell therapies requires us to extend treatment to solid tumors and to be able to substitute off-the-shelf standardized allogeneic T cells for the current individualized autologous products. Although the increased resources now committed to the field and the knowledge we have already gained should both accelerate progress in these aims, cellular therapies will remain complex entities whose clinical behavior will continue to be rather unpredictable, even after extensive preclinical testing. For the foreseeable future, therefore, we will still need to conduct small-scale, data-dense, clinical studies. Almost certainly, these will remain iterative, with outcomes feeding back to the preclinical models and adapting the tactics used. This open-ended early development pipeline of uncertain cost and duration can be unendurable for any commercial entity. Consequently, early stage clinical implementation has been largely the province of academic investigators, allowing the therapeutic approach to be adequately derisked for industry.[4,5] Though there will be the temptation to short circuit this process and bring even early stage pre-clinical work directly into a commercial program, this will continue to be a hazardous strategy. Conversely, leaving a product too long in the hands of academia almost inevitably retards both the development of robust validated manufacturing and the conduct of rigorous pivotal clinical trials. The solution may come from earlier and closer collaboration between academia and industry, even though this may be hampered by clashes between two quite different cultures. Moreover, collaboration should be an ongoing process, with drug-regulatory approval processes modified to allow improved variants of a primary T cell therapy to be considered as amended versions of an established agent, rather than as an entirely new drug—analogous to the sequential versions of computer operating systems and cell phone apps. This "Version 2.0" strategy is not without risks but will be essential if product improvement is not to stagnate.

We also need to consider the clinical infrastructure required for optimal delivery of these newly developed cell therapies. Tisagenlecleucel has been proclaimed the first "living drug," but we should not allow this canny rebranding to obscure its many closely equivalent cell therapy antecedents, such as stem cell transplantation and associated T cell manipulations.[6–9] Should newer T cell therapies, such as tisagenlecleucel, be administered primarily at pre-existing stem cell transplant centers that already have in place the necessary physical and personnel infrastructure? Or should they be the province of newly trained general oncology practices? The outcome of this turf war will likely vary from institution to institution, but the Foundation for Accreditation of Cell Therapy (FACT) already has in place a set of standards for the conduct of cell therapies,[10] and, in the US at least, FACT approval may become required by third-party payers to ensure patients receive the safest and most effective treatment with T cell products. Ultimately, if the reach and effectiveness of immune-oncology in general becomes as broad as we hope, a separate subspecialty may be formed, able to integrate all available immunotherapy resources for each disease.

Economic considerations will also impact how widely and how well T cell immunotherapy is used, since these treatments represent a different model to conventional cancer drugs. Unlike standard chemotherapy, T cell drugs will remain costly to manufacture, will be administered only once or a few times, and will frequently be curative. If a company is to recoup the costs of development and ensure their expected return on investment, these agents will remain eye-wateringly expensive. Attempts at cost remediation will undoubtedly be made. Prices may be capped by payers, the manufacturers may charge only if the drugs are successful (as defined by the company!), or payers may agree to a reverse annuity, in which a payment is made for each year of life after treatment. No single approach will be universally adopted, depending instead on whether single or multiple payers are involved; the success rate of the therapy; the incidence of the disease; and the stage of the treatment (first-line or after relapse) at which the T cells are delivered. But, like any outcomes-based payment, fair value can only be assessed if we know the true cost:benefit ratio in terms of survival, quality of life, and total cost of both therapeutic and supportive-care treatment and if we can compare these data with the cost:benefit ratio of alternative therapies. This information will need to be obtained with a high degree of precision by Health Services researchers much earlier in the drug development

process than is currently the case and will enable companies to decide whether to proceed or return the T cell therapeutic to be developed and administered entirely by cellular therapy or stem cell transplantation centers.

Although profound research, clinical, and economic challenges remain before T cell products will be broadly used for cancer therapy, the licensure of tisagenlecleucel clearly is a genuine moon-shot for our time. With sufficient resources, creativity, and wisdom, there is every reason to hope we will indeed go further and take CARs to Mars.

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