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CAR T-cells: Driving in the Fast Lane

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Chimeric antigen receptor (CAR) T-cell therapy as a treatment modality has accelerated in a remarkable fashion in recent years and is now a standard of care for treating patients with relapsed and refractory diffuse large B-cell lymphoma (DLBCL) and relapsed pediatric and adolescent B-cell acute lymphoblastic leukemia (B-ALL). This dramatic progress in the CAR T-cell field has been summarized in recent publications in HemaSphere.[1–8] These articles have comprehensively reviewed the substantial successes of CAR T-cell treatment as well as the potential for the future, but have also highlighted toxicity and future challenges.

The success of CAR T-cell therapy has not only been due to technological advances allowing for the manufacture of these cells; treatment with CAR T-cells has been effective in populations of patients where other treatments have been unsuccessful. In DLBCL, patients with refractory disease who have a very poor prognosis were the initial cohort to be treated with CAR T-cells. In a prior analysis of 861 patients treated with standard chemotherapy, the objective response rate to the next line of standard therapy was only 26% with a complete response (CR) rate of 7%.[9] The median survival for patients was only 6.3 months with only 20% of patients still alive at 2 years. It was in this very poor prognosis group of patients that CAR T-cell therapy showed very high and durable responses. Similarly, pediatric and adolescent patients with relapsed or refractory ALL have a very poor outcome. In a review of 313 patients, CR rates for patients in second or subsequent relapse were only 40% and the disease-free survival for patients in CR2 and CR3 was only 27% and 15%, respectively.[10] It was these challenging subpopulations of ALL patients who received CAR T-cells and in whom substantial and durable responses were seen.

This remarkable efficacy of CD19-directed CAR T-cells in DLBCL is well highlighted in a review article by Hopfinger et al.[2] Overall, response rates in the order of 50% to 80% were seen in patients with relapsed and refractory DLBCL and durable CRs have persisted in approximately 40% of patients treated. A further encouraging aspect of CAR T-cell therapy is that it has resulted in durable CRs in patients with relapsed double and triple hit lymphomas. These promising results have resulted in the approval of tisagenlecleucel and axicabtagene ciloleucel for the treatment of patients with this disease. The promising results in relapsed and refractory patients have led to randomized trials comparing CAR T-cell therapy to stem cell transplantation in DLBCL patients in first relapse. Similar outstanding results have been seen in pediatric and adolescent patients with B-ALL as summarized in a review article by DiNofia and Maude.[3] CD19-directed CAR T-cell therapy has resulted in an approximately 50% to 60% relapse-free survival at 1 year based on multiple clinical trials done at various institutions. These results in B-ALL are notably better than those expected with typical salvage chemotherapy. Tisagenlecleucel has therefore received approval based on these encouraging results.[1]

The substantial progress has not been without some challenges. Toxicities from CAR T-cell therapy are well described in the review articles by Yáñez San Segundo et al and Borrega et al.[4,5] Based on the effects of depleting B-cells as well as the activation of T-cells by the chimeric receptor, multiple toxicities including cytokine release syndrome (CRS) and neurotoxicity have complicated administration of these products. While this was originally a significant challenge, comprehensive guidance has now been provided on how to manage these complications. Careful monitoring and early intervention has made a substantial difference to the incidence and severity of these problems. While management of these issues is much improved, as pointed out by Borrega et al in their review,[5] more needs to be done to better understand the mechanism of these toxicities and define the population of patients in whom they are more likely to develop. With more patients treated in real life practice outside of clinical studies, prolonged cytopenias and infections are an emerging clinical problem requiring attention. As we move forward in this field, management and prevention of side effects and complications will need to be an important area of focus.

While it may have felt in recent months that CAR T-cell therapy has been in the fast lane as regards its development, the road ahead may be somewhat less conducive to speedy progress. As comprehensively reviewed by Holzinger et al,[6] new designs of CAR T-cells are being explored. This includes T cells redirected

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for universal cytokine-mediated killing (TRUCKs), bispecific CAR T-cells, conditional CARs, and armored CAR T-cells. Future perspectives include not only improving the CAR T-cell product or giving CAR T-cell products in combination with other agents,[7] but also developing CAR T-cells with efficacy against myeloid and T-cell malignancies as well as solid tumors.[8] Furthermore, it will also be important to protect the CAR T-cells from immune suppression as they enter the tumor microenvironment. Development of new cellular products and in particular "off the shelf" CAR T-cells is likely to take time and it may take a while before these therapies are available for routine clinical use.

Overall, there is substantial enthusiasm for the use of CAR T-cells to treat various hematological malignancies and solid tumors. Phenomenal progress has been made to date in providing this effective therapy for use in patients. As one looks to the future, not only will it be important to optimize the current CAR T-cell approaches but it will be important to develop the next generation of CAR T-cells. It will also be critically important to develop strategies for financial compensation for these treatments. All told, the future for CAR T-cells is very bright and the hope is that we can continue to speed ahead and make progress in T-cell treatment of patients with malignancies.

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