Immunotherapy Approaches in T-Cell Lymphoma: Highlights From SOHO 2021

At the 2021 SOHO Annual Meeting, Maksim Mamonkin, PhD, of Baylor College of Medicine, reviewed progress in immunotherapy for T-cell lymphoma. **Kelly Valla, PharmD, BCOP**, of Winship Cancer Institute of Emory University, discusses key insights from this session for advanced practitioners.

Unique challenges have prevented the type of fruitful development of chimeric antigen receptor (CAR) T-cell therapies for T-cell non-Hodgkin lymphomas (T-NHL) paralleling those used in B-cell malignancies. Fratricide and the risk for T-cell aplasia dominate the issues researchers face since targetable antigens are commonly shared between both normal and malignant cells (Fleischer et al., 2019; Scherer et al., 2019). Although B-cell aplasia is a risk for the CARs licensed for use in the B-cell lymphoma space, the degree of immunosuppression resulting from dampening normal T-cell function would have more devastating consequences. Focusing on antigens with restricted expression, such as CD30, could eliminate these obstacles. Unfortunately, this approach comes at the cost of limiting the number of patients who may benefit given the heterogeneity of this group of diseases. Conversely, targeting pan-T-cell antigens broadens applicability across T-NHL subtypes, but in doing so requires addressing the concerns of fratricide and T-cell aplasia.

Several CAR platforms utilizing pan-T-cell antigens are currently being evaluated in early-phase clinical trials, primarily targeting CD5 or CD7 (Gomes-Silva et al., 2017; Hill et al., 2019; Mamonkin et al., 2015). Interestingly, CD5 CARs are only subject to transient fratricide as a result of prompt downregulation of the target antigen on the CAR cells following transduction (Mamonkin et al., 2015). This phenomenon appears to be dependent on the selected costimulatory domain as evidenced by limited CAR T-cell expansion when substituting 4-1BB for CD28 due to an increased incidence of fratricide (Mamonkin et al., 2018). Utilizing a Tet-Off expression system to control CAR expression can circumvent this issue while preserving the enhanced CAR persistence associated with use of the 4-1BB costimulatory domain. Avoiding this self-killing mechanism is also possible by employing gene editing technologies, such as CRISPR-Cas9, to knock out the target antigen from the engineered CAR T cells; proof of this concept has been performed for both CD5 and CD7 CARs in preclinical models (Chun et al., 2020; Gomes-Silva et al., 2017; Raikar et al., 2017). An added benefit to using this maneuver is the potential to produce safe off-the-shelf allogeneic CARs, thereby reducing the risk of tumor-contaminated products and expediting access to these critically important therapies (Cooper et al., 2018). Protein expression blockers (PEBLs) impair cell mem-

J Adv Pract Oncol 2022;13(suppl 1):31–33
https://doi.org/10.6004/jadpro.2022.13.1.16

brane localization by anchoring antigens of interest in the endoplasmic reticulum and serve as another novel method to curb fratricide (Kamiya et al., 2018; Png et al., 2017).

Key Points

- Researchers are investigating the use of pan-T-cell antigens, primarily CD5, to develop CAR constructs for T-cell lymphoma.
- While CAR T-cell therapy for T-cell lymphoma is not yet ready, it is important for advanced practitioners to keep up with the latest data and availability of clinical trial opportunities.
- Advanced practitioners should keep an eye on not only acute but also long-term toxicity data, as well as further information on how best to position and sequence therapies.

CLINICAL TRIAL FINDINGS

First-in-human trials for CD5 and CD7 CAR constructs developed at Baylor University are already underway (ClinicalTrials.gov, 2021a, 2021b). The MAGENTA study (NCT03081910) reported initial results of their CD5-directed CAR as a bridge to allogeneic stem cell transplant in patients with T-cell acute lymphoblastic leukemia and T-NHL at the American Society of Hematology annual meeting in 2019 (Hill et al., 2019). Updated data presented at the 2021 SOHO meeting further illustrate the safety in the T-NHL cohort. Dr. Mamonkin described factors that appear to impact efficacy. An overall response rate of 44% in the 9 patients with T-NHL treated thus far exemplifies the potential utility of this treatment option. Importantly, low rates and primarily low grades of both cytokine release syndrome (CRS) and neurotoxicity were seen in this heavily pretreated population of T-NHL subtypes, which included patients with cutaneous T-cell lymphoma (CTCL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma (PTCL), and adult T-cell leukemia/lymphoma (ATLL). Expansion kinetics were favorable and similar across dose levels tested peaking around 1 to 4 weeks from infusion and subsiding at around 8 weeks. Neither expansion nor persistence of these CARs appeared to correlate with an improved clinical effect, but an abbreviated manufacturing time positively influenced response. Reducing time to cryopreservation of engineered CARs down to 3 to 5 days (from 6 to 7 days) restricts terminal differentiation and retains homing markers CD62L and CCR7. These features preserve potency of the CAR T cells and allow for more efficient trafficking to lymph nodes.

Reducing the risk of T-cell aplasia, and thus potentially life-threatening infections, is the other key to successful application of CARs in T-NHL (Scherer et al., 2019; Fleischer et al., 2019). Selecting tumor-specific restricted target antigens is one way to sidestep this otherwise on-target, off-tumor toxicity. Reconstituting the immune system by performing an allogeneic stem cell transplant following CAR T-cell infusion is another solution and was the intended therapeutic path for patients on the MAGENTA study (Hill et al., 2019; Scherer et al., 2019; Fleischer et al., 2019). This maneuver may be effective, but is also invasive, costly, and not without inherent and significant risk. Fortunately, the CD5-directed CAR T cells used in MAGENTA have not been associated with notable instances of T-cell aplasia, despite reducing the overall quantity of normal circulating T-cells (Hill et al., 2019; Mamonkin et al., 2015). Nevertheless, optimizing CAR constructs to avoid risk of this off-tumor toxicity is an area of interest. Use of alternative methods, such as mRNA electroporation or adeno-associated viral-vectors, to replace retroviral vectors for CAR delivery during manufacturing leads to transient expression following infusion and limits ongoing T-cell elimination following initial anti-tumor effect (Fleischer et al., 2019). Incorporation of suicide genes or switches to control CAR expression is also a potential solution. This method would allow for clinicians to exploit functionality more precisely and individualize care.

The Advanced Practitioner Perspective

Rapid evolution of the field of cellular therapy demands continuous learning from advanced practitioners. Finding a balance for avoiding fratricide and T-cell aplasia while ensuring a positive therapeutic impact among such a heterogeneous set of diseases represent the key challenges to bring this breakthrough therapy forward for T-NHL. Understanding underlying concepts and engineering challenges can

strengthen how patients are ultimately managed in everyday practice. Preparing for translation of these investigational agents to clinical practice is well within the scope and expertise of advanced practitioners. In the case of CAR T-cell therapy for T-NHL, providers must continue to follow the impact across disease subtypes along with identifying the most effective tactics to mitigate long-term toxicities. Keeping up with data in this niche space primes the advanced practitioner to anticipate needs for patient education and logistics for peri- and post-infusion care.

Disclosure

Dr. Valla has served on the speakers bureau for BeiGene.

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