The path forward for CD19 CAR-Ts in heme malignancies?

The approval of two autologous CD19 CAR-Ts has been a game-changer to show transformative outcomes in hard-to-treat patients with B-cell malignancies which otherwise lacked options. Though there is still plenty of room for improvement as other 'off-the-shelf' approaches are vying for entry, many new strides have been taken since the first approval.

New future strategies

Strategies are underway to create designer CAR-Ts with clinically important characteristics.

- The duration of CAR-T cell persistence is required for cure, though remissions continue after disappearance of functional CAR-Ts cells.
- The evidence suggests that the hinge and transmembrane domains of CARs can affect the function of CAR-T cells. T-cells expressing CARs with CD8α hinge and transmembrane domains showed lower levels of cytokine release[1,3.] The CAR design impacts CAR-T cell function to drive clinical outcomes related to efficacy and toxicities such as CRS and neurologic toxicity.

Understanding the mechanism of resistance

There is a currently a high unmet need to reduce the risk of relapse with CAR-Ts. The target antigen is critical for T-cell therapies such as CD19 that is uniformly expressed by most B-cell lymphomas and leukemias[1,3].

- The CD19 (-) negative relapse due to antigen loss is common post CAR-T therapy and has been attributed to resistance/relapse especially in patients with high tumor burden in ALL. However, CD19(+) positive relapses have also been observed due to B-cell aplasia, exhaustion of products and shorter CAR persistence
- The current PFS with CAR-Ts is ≤50% in B-cell malignancies[1,2]. Targeting multiple antigens is a potential strategy to improve CAR-T efficacy by overcoming antigen loss and resistance such as bispecific anti-CD19/CD22 CAR for ALL, anti-CD19/CD20 CAR for B-cell lymphomas, or identification of novel antigens such as CD22 CAR-T which is active in both CD19- and CD19+ B-ALL relapses and may help improve long term outcomes
- The increasing trend of transplant post CD19 CAR-T therapy has also shown improved event-free survival in children and AYA ALL compared to older patients and could be an effective way to reduce the risk of relapse[2]. Though, the durability of CD19 CAR-Ts in DLBCL is more compared to B-ALL, similar strategies to overcome resistance are needed for DLBCL too.

CAR-T costs, patient management & policy implications

The high price tag of CAR-T therapies is a critical barrier to wider adoption.

- The trend of decreasing admissions, ICU admissions and length of hospital stay has been observed for pediatric ALL[4,5]. The inpatients and ICU resource utilization analysis within 30 days of CD19 CAR-T infusion in ALL patients treated on clinical trials, or with approved products from 2012-2019 suggested that proportion of patients admitted to hospital/ICU and cumulative inpatient LOS has decreased over the last 7 years.
- A recent analysis showed over 90% pediatric ALL patients safely received CD19 CAR-T in the outpatient setting[5]. The outpatient administration of CAR-T with Lisocabtageme maraleucel was also considered safe and effective in R/R DLBCL based on TRANSCEND NHL 001, PILOT and OUTREACH studies.
- The CMS's recent modernization of the current payment system is likely to make the high cost CAR-T therapies affordable and accessible for patients by increasing the NTAP cap from 50% to 65% of estimated cost. The future evolution of policy decisions will include considerations regarding the durability of CAR-T therapy, management of toxicities, future combinations with other high cost therapies to attain cure, considering new DRG, better payment methods that can increase the outreach of transformative therapies to broader patients

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