EUROPEAN HEMATOLOGY ASSOCIATION

Acute lymphoblastic leukemia - The worst and the best - Section 2

Immunotherapy for acute lymphoblastic leukemia: From biology to the clinic and back

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Take-home messages

- CD19-targeted immunotherapy has been highly successful in the treatment of relapsed and refractory ALL and can generate durable remissions.
- A substantial number of patients will relapse due to either leukemic resistance (antigen loss) or immunotherapeutic failure.
- CD22 is another validated ALL target creating opportunities for multispecific targeting with the potential to reduce antigen-loss relapses.

There has been a recent explosion of successful immune-based therapeutic options in oncology, including the approval of immunotherapeutic agents for treatment of multiple types of cancers, such that immunotherapy can now be considered a part of standard cancer treatment.[1] This review will summarize the status of immunotherapeutic approaches for the treatment acute lymphoblastic leukemia. Dramatic therapeutic success has been achieved with agents that block or inhibit negative regulators of the immune response (immune checkpoint inhibitors).[2] Initially demonstrated with anti-CTLA4 in melanoma, this approach has now extended to other immune regulatory pathways such as PD1/PDL1 and to other types of cancer. Unfortunately, the preliminary experience with these agents in pediatric cancers and for many hematologic malignancies has been disappointing. The reasons for this have not been entirely elucidated but a prevailing thought is that pediatric cancers have less neoantigens to which pre-existing immune responses can be 'unleashed' through checkpoint inhibition[3-5] due to the low nonsynonymous mutation rate in pediatric cancer compared to adult epithelial malignancies.[6]

One strategy to overcome a lack of natural T cell immunity is to 'redirect' the specificity of immune cells towards tumor-expressed targets using agents that bridge immune cell receptors and malignant cells. A bispecific immune engager that binds CD3 on T cells and CD19 on B cell malignancies has been successful in both adult and pediatric B lineage acute lymphoblastic leukemia (ALL) and has been approved for the treatment of relapsed and refractory patients.[7] Other multi-specific immune engagers are currently being tested in clinical trials against a number of other hematologic malignancies such as acute myeloid leukemia (AML), as well as engagers of other immune effector cells such as NK cells.

A second redirection strategy is to genetically engineer immune effector cells to artificially express a receptor that recognizes a tumor antigen. Chimeric antigen receptors (CARs) contain a domain that binds a cell surface antigen (typically a via an antibody-derived sequence) combined in the same construct with T cell receptor (TCR) signaling machinery (Figure 1A).[8] Second generation CARs contain both a TCR signaling sequence (typically CD3zeta) and a co-stimulatory signaling domain (for example, derived from CD28 or 41BB). CARs require cell surface expressed targets but have the advantage over TCRs of not being restricted by the major histocompatibility complex such that they can be used in all patients. Both TCR- and CAR-based gene-modified T cell therapies are being tested in the clinic.[9,10]

Genetically engineered immune effector cells have now been generated successfully at clinical grade and in sufficient numbers for infusion as patient specific products across multiple clinical trials. The most dramatic example of success with this approach has been the use of T cells engineered to express a CD19-targeted CAR. Remissions were achieved in 60-80% of patients with relapsed or refractory B lineage ALL in multiple phase I clinical trials.[11] One lesson learned from this early experience with CARs is that the dose required for remission is remarkably small (typically $<10^8$ cells). This allows for a relatively short production time but response requires the ability for the T cells to expand dramatically after infusion. Based on the success with the CD19 CAR in phase I trials, phase II trials are underway. Thus far, preliminary data has demonstrated comparable response rates in phase II trials to initial phase I studies and trials incorporating CD19 CAR T cells early in ALL therapy based on standard risk assessment are being planned.

Longer term follow-up of patients treated with CD19 CAR suggests that relapse may occur in 1/3 to 1/2 of patients

achieving remission (Figure 1B). One pattern of relapse seems to result from lack of CAR persistence. Although optimal length of CAR T cell persistence has yet to be defined, some centers consider 3-6 months to be a reasonable target. For patients with sub-optimal persistence, strategies to modulate T cell behavior and immune biology would be predicted to improve durability of remission. Studies are underway to look for markers of inferior T cell quality both in the product and in patients after infusion. Approaches to improve persistence such as cytokine administration or boost vaccines are also being explored.

The second pattern of relapse occurring following remissions induced by CD19 CAR and CD19 bispecific immune engagers is loss the targeted CD19 antigen as an example of immune escape. Interestingly, many of these relapses may not involve loss of the full CD19 protein but rather an alternative post-transcriptional splicing event such that the RNA transcript no longer contains the exon encoding the targeted epitope.[12] Another mechanism of immune escape that was initially identified in a murine model involved lineage switch of a pre-B cell ALL to a myeloid phenotype occurring in the presence of persistent CD19 CAR.[13] This mechanism of resistance has also been seen in patients with MLL-rearranged ALL following CD19-targeted immunotherapy, suggesting recapitulation of leukemia biology under lineage-targeted immune pressure.[14,15]

CD22 has been well validated as an alternative B cell restricted ALL target based on high response rates using a CD22-targeted immunotoxin conjugate (Inotuzumab Ozogamycin).[16] Success with a second CAR targeting CD22 has recently been reported with a 75% remission induction, including patients with CD19 antigen loss after CD19-targeted therapy. This experience is proof of principal of success with CARs targeting other antigens besides CD19 and that patients relapsing with resistant leukemia after immunotherapy can be salvaged with an alternative immunotherapy. Although durable remission is possible after the CD22 CAR, relapse due changes in CD22 expression occurred. Interestingly, rather than complete loss of CD22, most patients relapsed with leukemia that had reduced density of CD22 expression.

Although recent experience with immunotherapy for hematologic malignancies has been promising, there are a number of

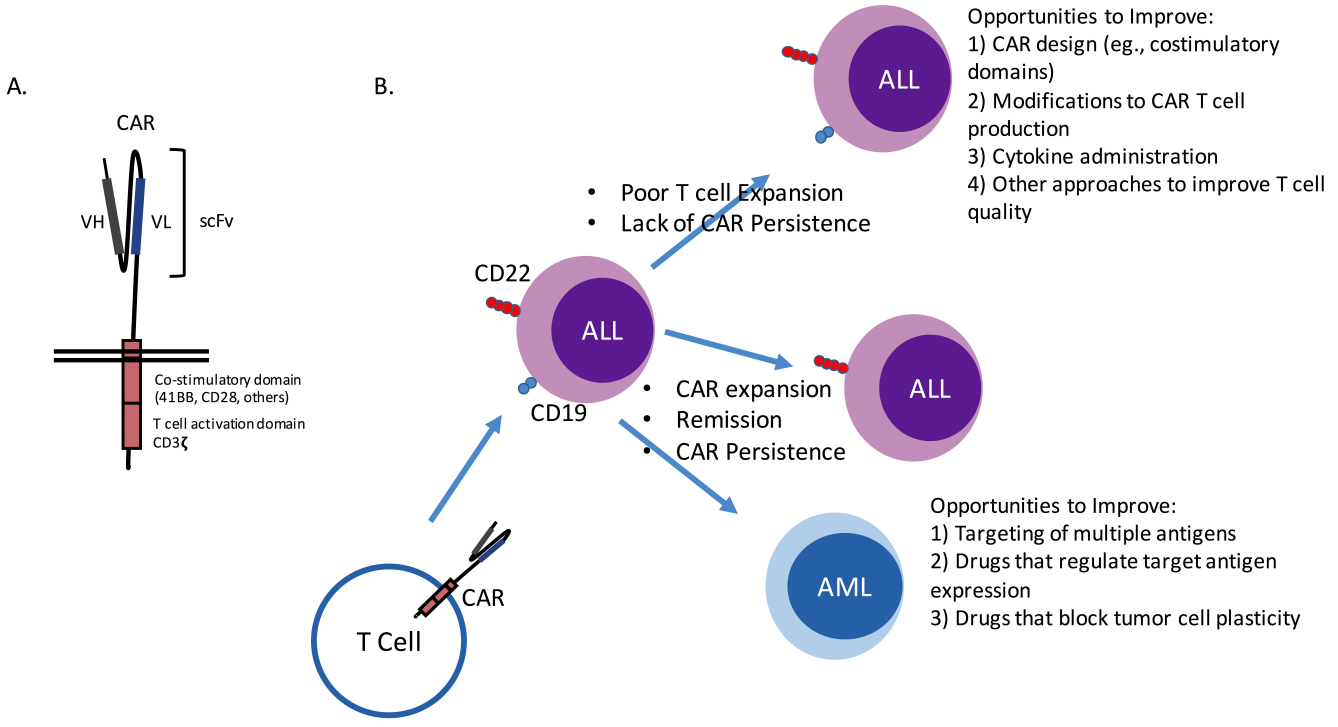

Figure 1. A) Schematic of a chimeric antigen receptor. B) Mechanisms of relapse after CAR therapy for ALL.

challenges. Multi-specific immune engagers and genetically modified T cells cause cytokine release syndrome a toxicity resulting in substantial morbidity and mortality can occur. In addition, significant neurotoxicity has been seen in some trials although the severity seems to be less in children than in adults. A better understanding of the pathophysiology of both CRS and neurotoxicity will be required to more safely administer these agents. For B lineage ALL, addressing antigen loss relapse will be important to improve durability of remissions. With recent identification of an active CAR targeting CD22 one approach would be to target 2 antigens simultaneously.[17,18] A CD19xCD22 bispecific CAR will enter clinical trials in the near future. Finally, although trials with CARs targeting AML are underway, it remains to be seen whether the success of CAR T cells in ALL can be reproduced in other hematologic malignancies.

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