Chimeric antigen receptor therapy for T-cell acute lymphoblastic leukemia: finally catching up with B-cell leukemia?

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Chimeric antigen receptor (CAR) T-cell therapy is a treatment in which an artificial gene causes expression of a CAR within T cells. There are currently six CAR T-cell products approved by the Food and Drug Administration in the United States and by the European Union, targeting either CD19 or B-cell maturation antigen (BCMA) for several hematologic indications, all involving B-cell malignancies. These therapies have reshaped clinical practice leading to deep and sustained responses in patients diagnosed with these malignancies.

Until recently, the major advances in the therapy of acute lymphoblastic leukemia (ALL) have been confined, almost exclusively, to the B-lineage variant. Experience from more than a decade of therapy with rituximab taught us, rather surprisingly, that prolonged B-cell aplasia and hypogammaglobulinemia can be tolerated. This was a crucial forerunner to the development of bispecific antibodies targeting CD19 (as in blinatumumab) or antibody-drug conjugates targeting CD22 (as in inotuzumab ozogamicin) and more recently CAR T-cell therapy targeting CD19 or CD22 in leukemia and lymphoma. These were dramatic scientific and clinical developments that altered the landscape and standard of care for patients with B-cell leukemia and lymphoma. In contrast, T-cell leukemia and lymphoma, with a grim prognosis, appeared to be left behind. How could one target a T-cell antigen with a CAR T cell without committing 'fratricide'? And, recalling the difficulty in developing CAR T cells for acute myeloid leukemia due to the inevitable neutropenia, how would one tolerate CAR T cells for T-ALL with the predicted lymphopenia?

In this issue of *Haematologica*, Oh *et al.*[1] beautifully review the development and potential of applying CAR T-cell therapy to T-cell ALL with a focus on CD7 as an ideal target. The choice of the target antigen is extremely important to improve both the efficacy and safety of CAR T-cell therapy. CD7 is the most widely explored and presented as a selected target due to its consistent expression in the majority of patients with T-ALL and, particularly, in refractory subtypes such as early T-cell precursor ALL. Thus, most CAR are designed to target CD7, with additional studies targeting mainly CD5 and CD38.

There are several inherent challenges associated with redirecting one T cell towards another T cell (Figure 1). The first challenge is based on the fact that rarely is there a tumor-specific antigen to target, so one uses a tumor-associated antigen, present on normal cells as well as malignant cells. Furthermore, in the context of T-cell malignancies, effector cells and target cells express the same antigens. Thus, CD7 targeting by CAR T cells will result in cytotoxic killing, a phenomenon widely known as "fratricide". To overcome this challenge some groups are exploring ways to reduce or eliminate the target expression on T cells, either by blocking the protein expression on the surface, selecting for a T-cell population not expressing the target antigen, or by genetic editing of the CAR T cells. Although reduction of target antigen expression seems rational, some groups have shown impressive clinical responses while avoiding such manipulations in T-cell leukemia and lymphoma.[2,3] This could be explained by a reported detection of some cells transduced with a CAR that would result in masking or intracellular sequestration of CD7 expression, leading to resistance to fratricide.[3] On this basis, one could hypothesize that with some tumor-associated antigens, the fratricide would be minimal and not harmful for the final CAR T-cell product.

The second challenge is the risk of leukemic contamination of the final product. In 2018, a group from the University of Pennsylvania reported a dreaded complication following CAR T-cell treatment, defined as CAR-transduced B-cell leukemia (CARB) cells.[4] In that report, a patient with B-ALL

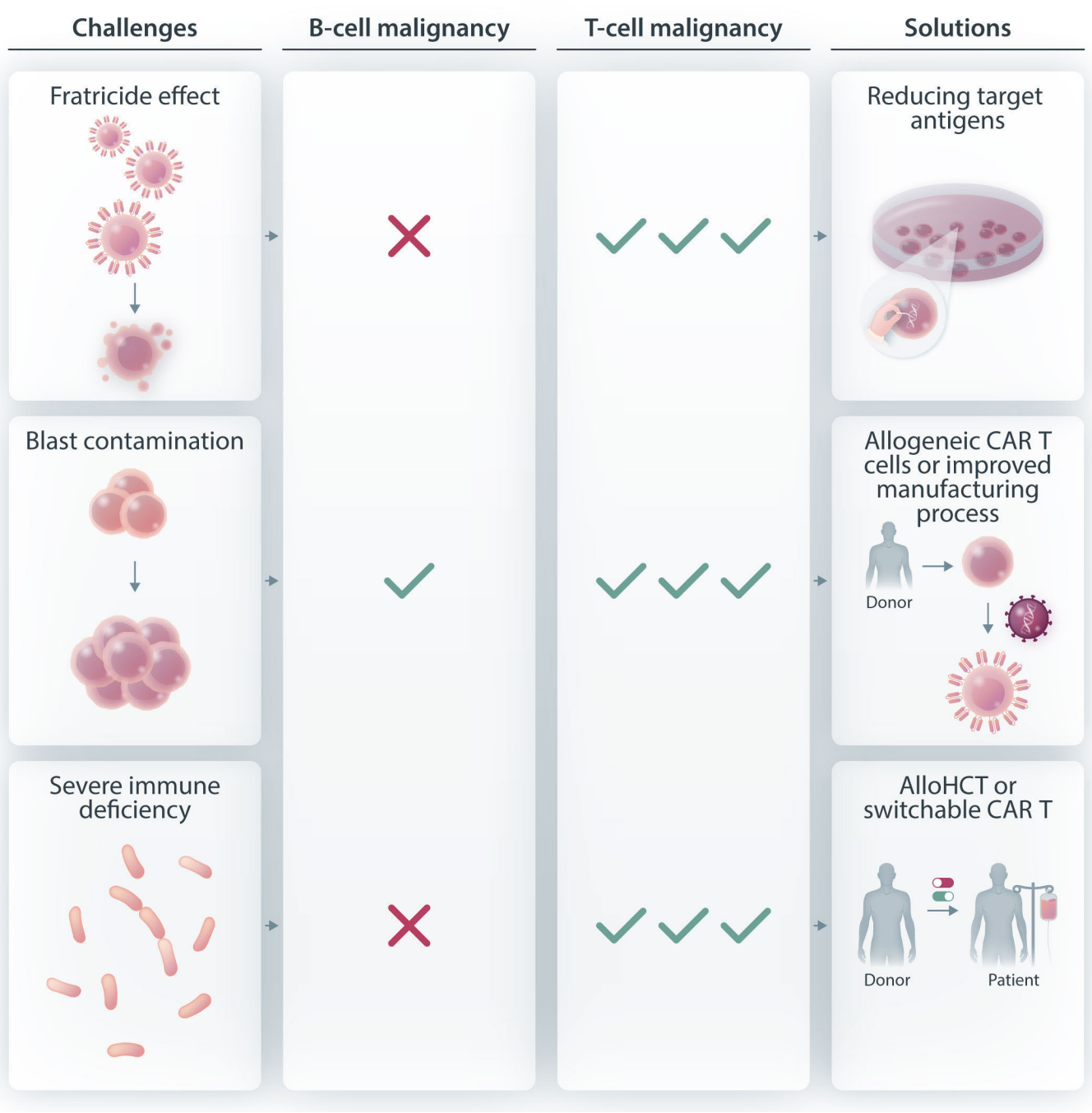

Figure 1. Unique challenges of developing autologous chimeric antigen receptor T cells for T-cell malignancies. There are several unique challenges presented by virtue of targeting T-cell malignancies using chimeric antigen receptor (CAR) T cells. Fratricide is described in the setting of T-cell malignancies but not in B-cell malignancies. This can be addressed by reducing or eliminating the target antigen from the surface of the T cells. Blast contamination can complicate any CAR T-cell therapy but is more prominent in the setting of T-cell acute lymphoblastic leukemia. This hurdle can be overcome by using allogeneic CAR T cells or by improving manufacturing techniques so that blast cells are certainly excluded. The risk of infections is greater with prolonged T-cell aplasia than with B-cell aplasia. This toxicity is reasonably well tolerated during CAR T-cell therapy targeting B-cell malignancies, with immunoglobulin supplementation for patients experiencing recurrent infections. However, there is no available therapy for prolonged T-cell aplasia. Potential ways to overcome this toxicity is by consolidative allogeneic hematopoietic cell transplantation or a switchable CAR T-cell platform. AlloHCT: allogeneic hematopoietic cell transplantation.

experienced an aggressive leukemia relapse 252 days following CAR T-cell administration with transduction of a single blast cell. This led to the generation of CAR19-expressing B-ALL cells that masked the CD19 antigen and created a CAR T-cell-resistant leukemia. This case emphasizes the need to improve manufacturing methods so as to exclude any possibility of product contamination by blast cells. Since this is particularly difficult to ensure in T-ALL, careful analysis of the final product is required. A potential approach to address this challenge is the utilization of allogeneic CAR T cells, with which there are, obviously, no concerns about blast contamination.

The third challenge involves the long-term and durable T-cell depletion associated with CAR T cells targeting the T-cell lineage (on-target, off-tumor). In B-cell malignancies, the depletion of B cells and hypogammaglobulinemia are manageable in most patients who do not experience serious infections or require immunoglobulin supplementation. Conversely, based on the evidence obtained in the setting of T-cell-depleted allogeneic transplants, reduced anti-microbial responses are expected and severe life-threatening infections are the rule. Moreover, T-cell aplasia is commonly accompanied by immune effector-cell-associated hematotoxicity, such as pancytopenia, developing after CAR T-cell

administration, further increasing the risk of infection. In order to circumvent this problem, subsequent allogeneic transplantation or "switching off" the CAR T-cell product upon malignant cell killing must be offered to ensure T-cell reconstitution. Nevertheless, in a recent study in which CAR T cells targeting CD5 were administered to nine patients with mature T-cell lymphoma,[2] two patients declined to proceed to allogeneic hematopoietic cell transplantation and, surprisingly, this was not associated with prolonged T-cell aplasia or severe infectious complications. Although hard to draw conclusions from two patients, this raises the issue of whether allogeneic transplantation is always critical for reducing prolonged T-cell aplasia. This is further emphasized in a report of manageable T-cell aplasia in 12 patients treated with CD7-CAR T cells not proceeding to allogeneic transplantation.[5] Irrespectively, the aggressive nature of the underlying disease may in and of itself mandate using CAR T cells as a bridge to transplantation. This is uncertain territory also in the setting of B-ALL, for which many more data are available. In other reports assessing CAR T cells for the treatment of T-ALL/T-lymphoblastic lymphoma, initial responses appear very promising, with an 85-95% complete response rate by day 28, but the durability of the effect is unknown since many of these patients underwent consolidative allogeneic hematopoietic cell transplantation.[3,5]

Currently, there are 16 CAR T-cell trials for T-cell malignancies listed in the ClinicalTrial.gov website, with eight of these trials actively recruiting patients. Eleven trials are in China, three in the USA and two in Europe. Most of these trials target CD7 (n=11), whereas other less common targets include CD5, CD1a, TRBC1, and OC-1.

Clearly, the field of CAR T-cell therapy for T-cell malignancies is evolving rapidly. While very significant obstacles persist, and we are still far from adopting such as standard of care, there is at last excitement and hope that we are getting closer to overcoming what hitherto appeared to be insurmountable.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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