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CLINICAL TRIALS AND OBSERVATIONS

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The quest for a cure in follicular lymphoma

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In this issue of *Blood*, Neelapu et al[1] report for the first time long-term results of treatment of patients with indolent lymphoma with axicabtagene ciloleucel (axicel). In the ZUMA-5 trial 127 patients with follicular lymphoma (FL) and 31 patients with marginal zone lymphoma (MZL) were treated and the primary and secondary end points, as well as some additional exploratory analyses, are reported after a median follow-up of 47.1 months. Not surprisingly, the overall response rate (ORR), the primary end point, remained unchanged (94% in FL; 77% in MZL). Similar to the situation in diffuse large B-cell lymphoma (DLBCL), obtaining a complete response is also of importance in FL, as two-thirds of patients achieving a complete remission (CR) were still in remission at the data cutoff, and the median duration of response (DOR) was only 5 months in patients who reached a partial remission.

Although the outlook for patients with FL has improved over the past decades, the disease is still considered incurable. In fact, the majority of patients will die due to the lymphoma.[2] Also, the immunosuppressive and DNA-damaging effects of therapy take their toll, as patients are at increased risk of developing a second primary malignancy.[3] The prognosis is particularly poor for the approximately 20% of patients who progress within 24 months after first-line immunochemotherapy (often referred to as POD24).[4] Thus far, the only chance of cure has been allogeneic stem cell transplantation, but this comes at the cost of high transplant-related morbidity and mortality. Will novel T cell–directed immunotherapies turn the tides for these patients and offer the outlook of a prolonged disease-free interval, or even cure?

In the wake of reports in DLBCL, results of clinical trials both with bispecific antibodies and with chimeric antigen receptor (CAR) T cells in indolent lymphoma are becoming available. Bispecific antibodies or T-cell engagers have the advantage of being available off-the-shelf, without the need of apheresis of T cells and the subsequent 3 to 6 weeks' manufacturing time. The first CD3xCD20 T-cell engaging bispecific antibody approved by the European Medicines Agency and the Food and Drug Administration (mosunetuzumab) was investigated in a phase II trial in 90 patients with relapsed or refractory (R/R) FL, with similar disease characteristics as patients enrolled on the ZUMA-5 trial. Here, the ORR was 80% and the CR rate 60%, with no significantly inferior results in patients with "high-risk" factors such as double refractoriness and POD24.[5] The median progression-free survival (PFS) was 17.9 months, but the follow-up period was still short (18.3 months). Regarding CAR T-cell therapy, 2 other trials in FL had more or less mature follow-up. For both products, tisagenlecleucel[6] (ELARA study) and lisocabtagene maraleucel[7] (TRANSCEND FL study), similar efficacy in terms of ORR and DOR to axicel was observed with a more favorable toxicity profile, especially with regard to high-grade neurotoxicity. In summary, response percentages and PFS are possibly more favorable with CAR T-cell strategies, although the reverse may be true for higher-grade toxicities. The extended follow-up data for axicel reported by Neelapu et al are encouraging, but several issues concerning T cell–directed immunotherapy need resolution to assess the balance between risk (and costs!) and benefit.

First, in the absence of evidence generated by randomized trials, the true impact of these novel therapies can only be estimated, and comparing the results of a novel therapy to real-world cohorts is inherently flawed. For example, in the SCHOLAR-5 study, the comparison arm for axicel included a substantial number of patients treated with a phosphatidylinositol 3-kinase inhibitor, a class of drugs that is now infrequently used in the treatment of FL.[8] Comparing the results with population-based data would be more valuable, even though the real-world treatment trajectory can be quite diverse and, in contrast to the situation in DLBCL, there is no standard treatment sequence for R/R FL. Second, considering the still short follow-up of the trials, the long-term efficacy is not known, with the PFS curve in none of the trials reaching a convincing plateau. Neelapu et al provide an initial answer to this conundrum with a competing risk analysis, in which indeed the risk of progression or death related to lymphoma seems to reach a plateau earlier than that of competing risks. Longer follow-up in larger numbers of patients will clarify what this really means for patients. Third, not all patients may need these novel strategies, as their outlook is also favorable with more conventional treatment strategies. For those,

the risk of short- and long-term toxicity may outweigh the gain. Specifically concerning are the risk of opportunistic viral infections, such as progressive multifocal leukoencephalopathy, and secondary myelodysplastic syndrome/acute myeloid leukemia. It does remain difficult to attribute the occurrence of these particular risks specifically to lymphodepleting chemotherapy/CAR T-cell therapy or to prior or later treatment lines. Improving our ability to discern patients with a low vs high risk of poor outcome is needed to better select patients for this treatment, which also comes with a great economic burden and is not yet widely available globally due to high costs, complex logistics, and limited manufacturing slots.

Last, there is a negative correlation between long-term remission and POD24 and/or high total metabolic tumor volume, a correlation that also holds for CAR-T cell therapy. Importantly, data from this trial confirm that the use of bendamustine, especially within 6 months prior to apheresis, can negatively affect the starting material and thus CAR T-cell function.

How can we further improve this treatment? Should we administer it as second- or third-line therapy, aim at reducing tumor volume by more aggressive bridging therapy, or find methods of better selection of patients? All of these are valid and open questions.

In conclusion, Neelapu et al show that CD19 CAR T-cell therapy provides a highly effective and relatively safe treatment strategy for patients with R/R FL, but transparent reporting of all long-term side effects and long-term efficacy is important. Several randomized controlled trials are currently ongoing. Our biggest challenge will be to assign CAR T its appropriate position in the treatment algorithm of FL, especially if cure ultimately may not be achieved.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Dao et al, page 507

Two to tango: engineered T cells against AML

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In this issue of *Blood*, Dao et al[1] present a new dual-antigen targeted engineered T-cell platform for safe and efficient T-cell therapy of acute myeloid leukemia (AML).

Development and clinical implementation of targeted T-cell therapy for AML has so far been impeded by the phenotypic similarities between malignant and normal myelopoiesis, the paucity of tumor-specific antigens, the complex bone marrow microenvironment, and AML disease heterogeneity. Now, Dao et al redirected T cells against Wilms tumor 1 (WT1) with a novel antibody T-cell receptor (AbTCR) construct and exploited CD33 as input to activate a chimeric costimulatory signaling receptor (CSR) to enhance specificity, safety and efficacy (see figure). From their phage-display library, the authors identified new antibodies (ESK2) recognizing the WT1 RMF (RMFPNAPYL) peptide/HLA-A*02:01 complex with enhanced specificity compared with their previously identified ESK1 antibodies. The fragment antigen binding regions of 2 lead candidates were linked to the constant chains of the γδ T-cell receptor (TCR) and expressed in a viral vector along with a CSR recognizing CD33 through a single-chain variable fragment (scFv) linked to CD28. When human T cells transduced with AbTCR + CSR encountered AML cells expressing WT1 (RMF)/HLA-A*02:01 and CD33, the T cells recognized both target antigens and received T-cell activation signals from the γδ TCR/CD3 complex (signal 1, by AbTCR) and CD28 costimulation (signal 2, by CSR) (see figure). Investigation of engineered T-cell function showed that AbTCR$^+$ T cells specifically recognized and killed WT1 (RMF)/HLA-A*02:01$^+$ AML targets and that both killing and interferon-γ production were increased on delivery of CD28 costimulation through the CSR (see figure). The CSR acted in *cis*, requiring both the WT1 (RMF)/HLA-A*02:01 complex and CD33 expressed on the same target cell. More important, no toxicity against normal