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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Hay et al, page 1652

Running the tank to empty: how far can the CAR go?

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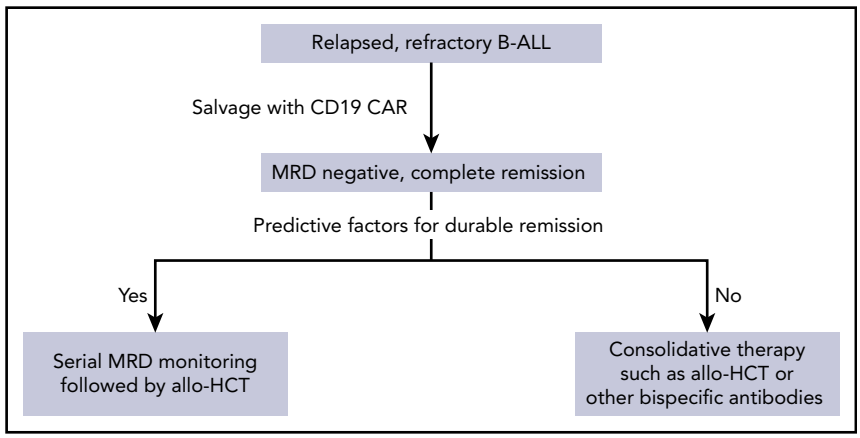
Although the importance of minimal residual disease (MRD) negativity has been well documented in acute leukemia, in this issue of *Blood*, Hay et al have specifically demonstrated its importance after chimeric antigen receptor (CAR) T-cell therapy, and have elucidated factors associated with durable event-free survival (EFS).[1]

CAR-T cells directed against CD19 have generated considerable enthusiasm with high rates of remission in heavily treated, relapsed, refractory patients. We now have an approved product as a salvage therapy for relapsed refractory B-cell acute lymphoblastic leukemia (B-ALL).[2,3] Depth and duration of such remissions, along with characteristics of relapses, are not well known, however. In addition, the role of allogeneic hematopoietic cell transplantation (HCT, considered a standard once complete remission [CR] is achieved) in the era of CAR-T is also not known. Hay et al address these 2 important questions in this study.

The value of MRD as an independent prognostic marker has been well established in B-ALL.[4] This is the first article that looks specifically at factors associated with durable EFS, including MRD negativity in patients with ALL undergoing CAR T-cell therapy. In this report, of 53 patients who received a CD19 CAR on a phase 1/2 clinical trial, 45 (85%) achieved MRD-negative status, as defined by high-resolution flow cytometry. After 2.5 years of follow-up, those patients had significantly better EFS and overall survival. The authors identified several factors that were associated with the likelihood of achieving MRD-negativity, including lower pretreatment lactate dehydrogenase, higher pretreatment platelet count, and use of fludarabine in the conditioning regimen, representing a mix of unmodifiable patient factors and likely suggesting a more aggressive disease and modifiable treatment factors. In addition, of those patients with an MRD-negative remission, absence of the index clone by immunoglobulin heavy chain deep sequencing was further associated with improved EFS.



Potential strategy for monitoring patients with MRD acute lymphoblastic leukemia after CAR T-cell therapy, based on predictive factors for EFS.

Despite such deep remissions, 22 (49%) of 45 patients who achieved MRD-negative CRs relapsed; 14 (64%) 22 had CD19-positive relapses and 6 (27%) 22 had CD19-negative relapses. Patients who received fludarabine conditioning and robust proliferation of CARTs subsequently had a CD19-negative relapse. Interestingly, all patients who did not receive fludarabine had lower persistence and peak of CART, and subsequently had a CD19-positive relapse. An increased magnitude of CAR-T expansion was associated with fludarabine use, suggesting that the kinetics of CAR-T expansion influences relapse phenotype.

At present, the role of consolidation with allogeneic HCT after CAR T-cell therapy for B-ALL is not clear. It is generally accepted as a standard of care, but its importance has not been universally demonstrated,[3] it is not known which patients will benefit most from consolidation, and it is not known whether it is necessary for all patients. In this report, 18 (40%) of 45 patients in MRD-negative remission subsequently went on to HCT. After adjusting for factors previously identified to be associated with achieving MRD negativity, the authors found that patients who underwent HCT had a lower risk for failure than those who did not. In addition, allo-HCT seemed to be beneficial in both low-risk and high-risk patients. However, there remains a subset of patients who enjoyed a durable EFS without undergoing HCT, suggesting that it is not necessary for all patients. Although small, the population of patients who achieved MRD negativity by immunoglobulin heavy chain deep sequencing is tantalizing, and it will be interesting to see whether this, in addition to other factors, can ultimately be used to identify patients who may do well without HCT. As the field matures, it will be of the utmost importance to continue to identify patients who will most likely benefit from further consolidation strategies, as well as those patients who are likely to do well without further therapy to avoid undue toxicity of allogeneic transplant (see figure). It is

incredibly exciting that we have reached a point where we can even start to have this conversation for patients with relapsed/refractory B-ALL.

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