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CAR-T for follicular lymphoma: are we good to go?

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In this issue of *Blood*, Ghione et al[1] have compared outcomes for patients with multiply relapsed follicular lymphoma treated with axicabtagene ciloleucel (axi-cel) in the ZUMA-5 study with those in the retrospective SCHOLAR-5 registry. Axi-cel was highly active in the ZUMA-5 population, with an impressive complete response rate of 79% and the median progression free survival not yet reached after 17.5 months of follow-up.[2] However, as a single-arm study, it is not possible to directly compare these outcomes with the plethora of currently available therapies, including various combinations of chemotherapy, anti-CD20 and bispecific antibodies, lenalidomide, phosphoinositide 3-kinase inhibitors, or enhancer of zeste homolog (EZH) 2 inhibitors. In the comparative effectiveness study, Ghione et al used propensity-scoring analysis on prespecified prognostic factors using standardized mortality weighting to match patients in the SCHOLAR-5 registry to those in the study. The authors charted marked improvements in response rate with axi-cel, as well as a notably improved time to next treatment and improved progression-free and overall survival, with a substantial 58% reduction in the risk of death (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.21-0.83).

The use of axi-cel for follicular lymphoma is accompanied by significant toxicities, with cytokine release syndrome in 78% of patients, which was grade 3 or worse in 6% of those treated. In the total trial population, 50% required treatment with tocilizumab and 5% needed vasopressors. Grade 3/4 neurological events were seen in 15% of patients, and grade 3 or worse infections were seen in 18%. As the authors note, it is not possible to directly compare these events to the historical controls.

The correlation between observational studies and formal randomized controlled trials (RCTs) has been debated for decades. In one study of 19 therapies examined across 53 observational studies and 83 RCTs, there was a high degree of correlation between the observational and randomized trials, with only 2 of the analyses showing an effect in the observational studies outside the 95% CI for the effect in the RCTs.[3] However, in a larger analysis restricted to oncology treatments, which compared 350 observational studies of 2 treatment regimens compiled from various databases versus 121 RCTs, there was no significant correlation between the HRs.[4]

Propensity-scoring analysis has been proposed as a method to simulate randomized controlled trials without the need for a contemporaneous control arm.[5] However, there is considerable debate as to how effective they are in this regard. Propensity scoring can adjust for a whole range of measured variables to decrease confounding but is unable to adjust for unmeasured variables. How can we be sure that the selected patients from a registry are truly comparable to those fit enough for inclusion in clinical trials?

Kumar et al compared the outcomes for patients in 141 RCTs across 8 cancer types versus matched patients in the National Cancer Database (NCDB).[6] When analyzed using propensity-scoring analysis, the correlation between HRs in the clinical trials and the database was low (r = 0.25; 95% CI, 0.09-0.40; P = .003). In 92 RCTs, there was no significant difference ($P \geq .05$) between the treatment arms, but the retrospective propensity-matched NCDB analysis in 59 of these studies (64%) showed significant P values. Of the 6 lymphoma studies analyzed, the HR was concordant in only 3 studies.

Despite these caveats, there are clearly patients with multiply relapsed follicular lymphoma for whom axi-cel will offer a significant benefit over existing therapies. Similarly, bispecific antibodies have shown comparable response rates in this population, with mosunetuzumab showing a complete response rate of 58% and overall response rate of 79% in a cohort of 90 patients with follicular lymphoma who had received ≥2 prior therapies.[7] The optimal sequencing of chimeric antigen receptor (CAR) T-cell therapy and the patients who benefit the most remain to be determined.

Ghione et al cite feasibility constraints of an RCT in multiply relapsed follicular lymphoma, but, while acknowledging the challenges, an RCT is essential to inform optimal use of axi-cel, as recently achieved in the setting of relapsed/refractory diffuse large B-cell lymphoma.[8] With improvements in the safe delivery of CAR T-cell therapy across populations and the impressive time to next treatment and overall survival advantages demonstrated in this comparative analysis, clinician and patient enthusiasm would be high, substantially improving the feasibility of conducting a phase 3 RCT, especially with a crossover design. Ideally, this would include a more racially diverse range of patients than the ZUMA-5 and SCHOLAR-1 cohorts, which were both >90% White. Based on these comparative effectiveness data, the number of patients needed to demonstrate superiority would not be large, and, given the multiple therapeutic options in the third-line setting, a comparator arm with physicians' choice for the standard of care would facilitate recruitment. RCTs are needed to formally compare the activity and toxicity of axi-cel with other approaches as we prepare to roll out this efficacious immunotherapy globally.

Conflict-of-interest disclosure: R.G. has received honoraria from Abbvie, Astellas, Janssen, MSD, Novartis, Otsuka Pharmaceutical, and Takeda. J.T. reports research funding

to institution from BeiGene, Celgene, Cellectar, Roche, PCYC, Takeda, and Janssen. ■

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DOI 10.1182/blood.2022017279

MYELOID NEOPLASIA

Comment on Tanaka et al, page 875

Mutant SF3B1 splices a more leukemogenic EVI1

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In this issue of *Blood*, Tanaka et al[1] identify a mechanistic link between the high co-occurrence of mutations in the splicing factor SF3B1, with inversion or translocation of chromosome 3 in acute myeloid leukemia (AML).

AML with chromosome 3 inversion (inv(3)) or translocation (t(3;3)) is a distinct disease entity in the current World Health Organization classification. Inv(3)/t(3;3) AML has a dismal prognosis because of low response to conventional chemotherapy and early relapse after bone marrow transplantation.[2,3] It is known that inv(3) and t(3;3) chromosome rearrangements cause marked overexpression of the zinc finger transcription factor, *EVI1*, because of enhancer hijacking of a *GATA2* distal enhancer.[4] Prior sequencing studies have identified co-mutation of *RAS* pathway genes and the splicing factor *SF3B1* in inv(3)/t(3;3) myeloid malignancies, however the mechanisms by which these additional mutations cooperate with inv(3)/t(3;3) to influence disease severity or susceptibility to AML-directed therapies are not well understood.[1,5,6]

In this study, Tanaka et al assembled a cohort of 109 patients with inv(3)/t(3;3) myeloid malignancies and found that *SF3B1* is the most frequently mutated gene in inv(3)/t(3;3) myeloid neoplasms (see figure). This finding is notable, as *SF3B1* is the most frequently mutated splicing factor in myelodysplastic syndrome (MDS). In contrast to patients with inv(3)/t(3;3) AML, patients with *SF3B1*-mutant MDS have a highly favorable prognosis in terms of overall survival and a low risk of transformation to AML.[7] Intriguingly, *SF3B1* mutations appear to be present in the dominant clone in both inv(3)/t(3;3) AML and *SF3B1*-mutant MDS, with a variant allele frequency of ~40% in both diseases. To determine whether *SF3B1* mutations affect disease progression in inv(3)/t(3;3) AML, Tanaka et al crossed transgenic mice expressing a humanized inv(3) allele with *Sf3b1*-mutant mice. They found that humanized inv(3)/*Sf3b1* double-mutant hematopoietic stem cells caused earlier lethality compared with humanized inv(3) alone when transplanted into wild-type recipient mice (see figure).

SF3B1 is a core component of the spliceosome that is critical for recognition of the branch point sequence within the introns of pre–messenger RNA (mRNA) and the early stages of splicing catalysis. Mutations in *SF3B1* cause the mutant protein to identify an upstream, "cryptic" branch point sequence, leading to the incorporation of intronic nucleotides into a misspliced mRNA transcript. In MDS, up to half of these aberrantly spliced transcripts are predicted to undergo nonsense-mediated mRNA decay (NMD), a quality control mechanism that eliminates misspliced transcripts that contain premature stop codons or frameshifts.[8,9] NMD-mediated degradation of aberrantly spliced transcripts from genes involved in heme biosynthesis is thought to partially explain the characteristic anemia seen in patients with SF3B1-mutant MDS.

In the current study, Tanaka et al identify a distinct functional consequence of mutant SF3B1-mediated aberrant splicing in inv(3)/t(3;3) AML. They observed that mutant SF3B1 expression in inv(3)/t(3;3) AML cell lines, patient samples, or humanized inv(3) transgenic murine cells is associated with the use of a cryptic branch point within intron 12 of the *EVI1* pre-mRNA. This leads to the generation of a novel isoform, *EVI1* + 18, that contains an additional 18 nucleotides between exons 12 and 13 (see figure). This 18-nucleotide insertion leads to a 6-amino-acid in-frame insertion at the C-terminal end of the 10th zinc finger of EVI1. Tanaka et al compared the genomic distribution of EVI1 and EVI1 + 18 in inv(3)/t(3;3) mutant AML cell lines expressing wild-type or mutant SF3B1 and found that EVI1 + 18 bound to a distinct group of genes associated with increased leukemogenesis including *MEIS1*. Moreover, they identified distinct biological effects associated with EVI1 + 18 expression. When overexpressed in primary murine hematopoietic cells, *EVI1* + 18 caused increased proliferation and increased clonogenic capacity compared with canonical *EVI1*.

The elegant functional studies performed by Tanaka et al suggest that *SF3B1* mutations in inv(3)/t(3;3) AML promote an even more aggressive leukemia phenotype caused by EVI1 + 18 mediated