necessary to sustain progress in our field.

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LYMPHOID NEOPLASIA

Comment on Di Blasi et al, page 2584

Post-CAR relapse in DLBCL: a fork in the road

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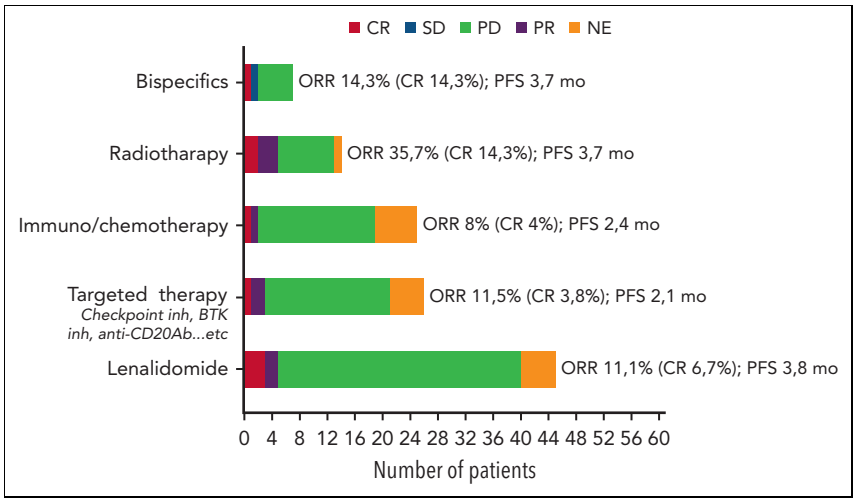
In this issue of *Blood*, Di Blasi et al highlight the transformational nature of chimeric antigen receptor (CAR) T cells, as well as the new unmet medical need in diffuse large B-cell lymphoma (DLBCL)—managing patients progressing after CAR T-cell therapy.[1] Before the availability of CAR T cells, patients with chemotherapy-refractory DLBCL had an extremely low likelihood of response to conventional therapy and a life expectancy in the range of 6 months. Today, CAR T cells induce complete responses in approximately half of these patients, and long-term cure is approximately 40%.[2] Di Blasi and colleagues use the French DESCAR-T (Dispositif d'Enregistrement et de Suivi des CAR-T) registry to assess the "real world" outcomes for 550 patients who received 1 of 2 available CAR T-cell products, axicabtagene ciloleucel or tisagenlecleucel, for multiply relapsed or refractory DLBCL.

Among patients included in the registry, most had high-risk age-adjusted international prognostic index scores and had received >3 prior lines of therapy. At a median follow-up of 8 months after CAR T-cell infusion, 57% of patients have not progressed. Although this number is likely to decline somewhat with ongoing follow-up, a significant proportion of patients will clearly achieve durable remission because most CAR T-cell failures occur within 6 months of therapy. Despite this optimistic finding, 238 patients (43%) have progressed, for whom there is no agreed upon standard of care.

The most commonly used systemic treatment after CAR T-cell progression in the DESCAR-T registry was lenalidomide (38%), followed by targeted therapies (21%), chemoimmunotherapy (20%), and bispecific antibodies (7%); an additional 11% received radiation therapy for localized progression (see figure). Response to post-CAR treatment was low at 14%, with only 7% complete responders, and was disappointing for all systemic therapies administered. The median progression-free survival (PFS) and overall survival (OS) were short at 3 and 5 months, respectively. On multivariable analysis, elevated lactate dehydrogenase (LDH) and ferritin were associated with inferior PFS, whereas progression within 30 days of CAR T-cell infusion, elevated LDH and C-reactive protein were all adversely associated with OS. No specific therapies were associated with an improved PFS by multivariable analysis, although interestingly lenalidomide was associated with improved OS (hazard ratio, 0.42; $P = .01$).

Among classes of treatments employed, chemoimmunotherapy produced the lowest overall response rate, which is not unexpected in a heavily chemotherapy pretreated population. These patients are also more prone to myelotoxic effects of cytotoxic chemotherapy, which in addition would further impair activity of any persistent CAR T cells. As such, alternate immunotherapies and targeted therapies hold greater appeal in terms of both efficacy and safety. The small number of complete responses observed with lenalidomide, bispecific antibodies, and targeted therapies, although disappointing, provide a welcome signal that patients can respond if given the optimal treatment. The challenge, of course, is identifying what that treatment is for any given patient.

Among 45 patients treated with lenalidomide, 5 responded, including 3 complete responses, suggesting that some tumors are particularly susceptible. This is consistent with recognized activity of lenalidomide in relapsed DLBCL, which appears to be most beneficial in activated B-cell (ABC)-like tumors.[3] The OS benefit for lenalidomide in this



Overall response rate (ORR), complete response (CR) rate, and median progression-free survival (PFS) after CAR-T relapse, according to treatment type. PR, partial response; SD, stable disease. See Figure 1 in the article by Di Blasi et al that begins on page 2584.

population, despite generally low rates of response, raises the possibility that lenalidomide may be contributing to immune activation, including potential stimulation of persisting CAR T cells, which could be blunting the rate of progression and thus allowing patients to live longer. Although this is entirely speculative, it reminds us that patients progressing after CAR T cells are distinct from CAR T-cell naïve patients, and that treatments that overcome CAR T-cell exhaustion and immune escape would offer unique appeal in the post-CAR population.

Targeted therapies accounted for the next most common class of therapy, with the most common agents being immune checkpoint inhibitors and ibrutinib, both of which are typically well tolerated in this heavily pretreated patient population. Immune checkpoint inhibition could be an appealing strategy to reinvigorate exhausted CAR T cells, but responses to programmed death (PD)-1 inhibitors as a class in the post-CAR setting have proven disappointing.[4] This may reflect that numerous immune checkpoints other than PD-1 mediate T-cell exhaustion, but selected populations may be enriched for exceptional responders to PD-1 inhibitors. One such subset is primary mediastinal B-cell lymphoma, which frequently carries amplifications of programmed death ligand (PD-L)1 and PD-L2, and for which PD-1 inhibitors have significant activity in the relapsed/refractory setting. Case reports demonstrate reexpansion of CAR T cells and durable responses to pembrolizumab in primary mediastinal B-cell lymphoma relapsing after CAR T-cell treatment, making this an appealing post-CAR treatment in this large B-cell lymphoma subtype.[5] Ibrutinib carries the greatest appeal in treating relapsed/refractory DLBCLs with molecular features associated with response, such as ABC-like cell of origin and mutations of CD79B and MYD88 on next-generation sequencing.[6]

Bispecific antibodies represent one of the most appealing treatments currently under investigation in relapsed non-Hodgkin lymphomas, and have proven responses in heavily pretreated and previously CAR T-cell exposed patients.[7,8] These agents are presently only available on clinical trials in DLBCL, so protocol participation is encouraged for eligible patients. Antibody drug conjugates are approved therapies with significant clinical activity in multiply relapsed DLBCL and can induce responses in patients progressing after CAR T cells. Polatuzumab vedotin,[9] targeting CD79B, and loncastuximab tesirine,[10] targeting CD19 (if persistent expression is confirmed at the time of post CAR T-cell progression), were not included in the DESCAR-T registry because of lack of availability at the time, but should be considered in patients without a compelling rationale for an alternative agent based on disease characteristics. Finally, radiation can be a valuable tool for localized relapse or palliation of discrete sites of symptomatic disease.

Ultimately, selecting treatment for patients progressing after CAR T-cell therapy today must be personalized and informed by multiple patient- and disease-specific factors, including histologic and molecular subtypes of disease, types of prior therapy, bone marrow function, and comorbidities. Further understanding of mechanisms CAR T-cell resistance will allow optimization of post-CAR treatment, and ideally reduce the incidence of treatment failure in the first place.

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MYELOID NEOPLASIA

Comment on Janssen et al, page 2594

An unexpected partnership targeting *FLT3wt* AML

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In this issue of *Blood*, Janssen et al[1] identified a unique mechanism by which gilteritinib added to the BCL-2 inhibitor venetoclax increased activity in FMS-like tyrosine kinase (FLT3) wild-type (*FLT3wt*) high-risk acute myeloid leukemia (AML) preclinical models and patients.

AML is a heterogeneous disease of hematopoietic stem cell malignancies characterized by the absence of myeloid differentiation leading to rapid expansion of leukemic progenitors ultimately causing bone marrow failure.[2] Outcome of AML is generally dismal owing to relapse or refractoriness of the disease to standard treatment approaches. Disease outcome is particularly poor for elderly patients deemed unfit for intensive treatment strategies.

BCL-2 dependency is a hallmark of most AML cells. The small molecule venetoclax targets BCL-2 selectively and stabilizes proapoptotic proteins.[3] Despite promising antileukemic effects in vitro, clinical testing of venetoclax as single agent yielded only modest activity in clinical trials of patients with AML.[4] However, the combination of venetoclax with the hypomethylating agent azacitidine showed a significant improvement in response and survival compared with azacitidine alone for elderly unfit patients with newly diagnosed AML leading to approval of venetoclax by the Food and Drug Administration and European Medicines Agency in this setting.[5] Despite the significant improvement in outcome, relapsed and resistant disease remains frustratingly frequent. Thus, new approaches are needed, as no standard treatment is available for those patients.

Failure and resistance to venetoclax treatment is mainly mediated by myeloid cell leukemia-1 (MCL-1) overexpression in AML cells.[6] Thus, targeting the BCL-2/MCL-1 balance is an attractive drug target in AML. Recently, small molecule MCL-1 inhibitors have been studied in clinical trials, but development has been hampered by dose-limiting toxicities, in particular, cardiac toxicity.[7]

Thus, novel strategies to target MCL-1 expression are urgently needed to avoid and/or to restore sensitivity of AML cells to venetoclax. Based on this rationale, the findings of Janssen and colleagues to indirectly target MCL-1 in *FLT3wt* AML cells and patients by combining venetoclax with gilteritinib are of great interest. Both drugs are approved with well-known toxicity profiles for patients with AML.

Gilteritinib is a highly specific inhibitor of *FLT3* mutations (*FLT3*$^+$), including internal tandem mutations, which are the most frequent mutation found in up to 30% of patients with AML, and tyrosine kinase domain mutations. The drug is already approved for the treatment of relapsed or refractory AML in the United States and Europe as a single agent.[8] Clinical trials combining gilteritinib and venetoclax for relapsed and refractory mainly *FLT3*$^+$ patients with AML are underway and have demonstrated feasibility and efficacy.[9] Targeting MCL-1 by the combination of gilteritinib and venetoclax has already been reported in preclinical models of *FLT3*$^+$ AML.[10] Efficacy of the gilteritinib-venetoclax combination was also suggested in *FLT3wt* cells, but the precise mechanisms of action remain unknown.[10]

The strength of the study of Janssen and colleagues is that they started by identifying the best partner for venetoclax by performing an unsupervised high-throughput ex vivo drug screen with venetoclax and 64 drugs targeting relevant pathways in myeloid malignancies in 31 samples of high-risk patients with AML, including samples from *FLT3*$^+$ patients. High risk was defined as either treatment-refractory disease or high-risk genetic status according to European Leukemia Net 2017 guidelines. This screen identified gilteritinib as the most potent partner of venetoclax together with the MCL-1 inhibitor MIK665, suggesting that targeting MCL-1 might be a possible mechanism of antileukemic action of gilteritinib in this setting. Surprisingly, gilteritinib combined with venetoclax yielded significantly higher synergy in AML *FLT3wt* samples, particularly in those with very poor-risk *TP53* mutations as compared with *FLT3*$^+$ patient samples.

To dissect the precise mechanisms of action of combination treatment with gilteritinib and venetoclax in *FLT3wt* AML, the authors identified by proteomic studies increased FLT3 pathway signaling (including RAF/MAP, FLT3, and MAPK1/MAPK3 pathways) in patient samples resistant to combined azacitidine and venetoclax treatment compared with those samples sensitive to azacitidine and venetoclax treatment, suggesting that increased FLT3 signaling is responsible for azacitidine-venetoclax resistance. In very elegant experiments, the authors were able to elucidate the