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LYMPHOID NEOPLASIA

Comment on Bethge et al, page 349

German CARs keeping pace

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In this issue of *Blood*, Bethge et al[1] present findings from the analysis of 356 patients treated with axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) chimeric antigen receptor (CAR) T-cell therapy for large B-cell lymphoma (LBCL) in a non-trial setting in 21 centers throughout Germany with a median follow-up of 11 months. While corroborating the excellent results of these therapies in a real-world setting with an overall response rate (ORR) of 65% and 12-month overall survival (OS) of 52%, they also add important insights into this growing standard-of-care literature. Their analysis is the first to report response to, rather than use of, bridging therapy as a predictor of outcome. Additionally, they report an adjusted 12-month nonrelapse mortality (NRM) of 5.5% in all patients, most occurring late (67%) and due to infection (62%). While their analysis invites a comparison between axi-cel and tisa-cel, differences between the patients being selected for, and the sites offering, each product result in biases that should preclude such a comparison.

This German study confirms similar ORR and OS outcome data from prior real-world studies (see table). Compared with pivotal studies of axi-cel[2] and tisa-cel,[3] the authors report a lower progression-free survival (PFS), which may reflect practices specific to the delivery of these therapies in Germany. Some of this heterogeneity in logistics, patient selection, and management could explain the higher rate of high-grade cytokine release syndrome (CRS) seen with tisa-cel (13%) and lower rate of high-grade immune effector cell associated neurologic syndrome (ICANS) seen with axi-cel reported here compared with previous real-world series (see table). Differences in toxicity incidence may reflect clinical heterogeneity of real-world subjects as well as differences in patient selection and the diagnosis/management of these toxicities between centers. Several centers offered only a single product, and differences between each center regarding eligibility criteria, referral patterns, and toxicity mitigation strategies could account for differences seen between products. Remarkably, despite these potential differences, efficacy outcomes for axi-cel and tisa-cel remain consistent with numerous other studies (see table), further confirming the transformative impact of these therapies for patients.

This study is the first of its kind to examine response to bridging and its association with outcome after axi-cel and tisa-cel. Prior studies have shown use of bridging therapy to negatively impact both OS and NRM, the latter largely through infections. However, in these series, the predominant bridging therapy was myelosuppressive chemotherapy in an already chemorefractory patient population given an absence of more effective options.[4] Bethge et al incorporate newer bridging options and report nonresponse, rather than use, as a predictor of negative outcome. With the increasing use of non-chemotherapy–based bridging options with activity in chemorefractory lymphoma and less associated myelosuppression (ie, polatuzumab and/or radiation), the negative associations between bridging therapy and survival may no longer be relevant. These findings, that response to rather than use of bridging is what matters, indicate that previous associations of bridging therapy with adverse CAR-T treatment outcomes may be skewed by ineffective and immunosuppressive bridging regimens. Future prospective studies incorporating modern bridging modalities are needed to further investigate this hypothesis.

Defining late infectious toxicity after CAR T-cell treatment and its impact on survival is an additional unique analysis offered by this study. While B-cell aplasia and prolonged lymphopenia and cytopenias are increasingly appreciated after CD19 CAR T-cell therapy, their impact on infectious risk and survival has been poorly defined. In this study, nearly two-thirds of the 5.5% NRM occurs late, after day 28, and most of those deaths are due to infection. Risk factors include prolonged neutropenia and high-grade ICANS, which raises important questions regarding the acute and long-term management and monitoring of these patients. High-grade ICANS may have been associated with increased steroid dosing, setting patients up for late infections; if true, more judicious use of steroids for high-grade ICANS would be warranted. Additionally, immunosurveillance may need to be more prescriptive, and infection prophylaxis and monitoring may need to be extended, when applicable, to address these risks.

Finally, this study notes some key differences between the two products with respect to efficacy and toxicity. In particular, ORR, complete response rate, and 12-month PFS were superior for axi-cel when compared with tisa-cel (74% vs 53%; 42% vs 32%; 35% vs 24%, respectively). On multivariable analysis, treatment with tisa-cel was associated with an inferior PFS. Tisa-cel, on the other hand, was associated with a lower incidence of CRS overall but not high-grade CRS, and ICANS overall as well as high-grade ICANS, and 12-month NRM (3.5% vs 10.4%). Given the lack of difference seen

Outcomes in patients with LBCL treated with standard-of-care treatments (axi-cel, tisa-cel) in non-trial retrospective analyses

	Bethge et al[1]		Jacobson et al[4]	Nastoupil et al[5]	Axi-cel CIBMTR[6]	Tisa-cel CIBMTR[7]	CAR T-cell Consortium[8]		UK 2019[9]		UK unfit 2021[10]	
Product	Axi-cel	Tisa-cel	Axi-cel	Axi-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel
No. treated	173	183	122	275	533	155	158	86	62	29	25	28
ORR/CR (%)	74/42	53/32	70/50	82/64	74/54	62/40	75/53	59/42	37/21	29/17	47/45	
6-mo ORR (%)	NR	NR	41	NR	NR	34	~51	~35-40	~35-40		41	
CRS (%)	81	65	93	91	83	45	85	41	NR		85	
Gr 3+ CRS (%)	10	13	16	7	9	5	8	1	11		2	
ICANS (%)	44	22	70	69	53	18	53	14	NR		40	
Gr 3+ ICANS (%)	16	7	35	31	17	5	33	0	13		11	

CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; NR, not reported.

in OS, one could argue that the improved efficacy seen with axi-cel could be deprioritized over the improved late toxicity profile seen with tisa-cel. We strongly caution against such a comparison and interpretation, however. First, in light of new effective but not definitive therapies for cases of multiply relapsed LBCL, 11 months may not be long enough to assess an OS difference among patients with relapsing LBCL. Second, and as noted by the authors, there are differences in the populations treated with axi-cel and tisa-cel based on patient characteristics that have previously been shown to be correlates of poor response to therapy as well as presumed differences in clinical practice ranging from patient selection to toxicity management and surveillance among sites that treat with only a single product, leading to biases that cannot be controlled for or defined.[4,5]

In summary, Bethge et al present a well-designed, large, multicenter, retrospective study of real-world use of axi-cel and tisa-cel in LBCL in Germany. Their data add novel insights to the field, particularly with regards to response to bridging therapy as a predictor of outcome and characterization of late infectious complications. These data highlight the need for prospective studies of novel bridging regimens as well as investigation into methods to mitigate late infectious mortality. We caution against drawing conclusions regarding the differences between axi-cel and tisa-cel outcomes given inherent biases outlined above; however, the data here once again recapitulate the previously described clinical activity of these products in LBCL.

Conflict-of-interest disclosure: C.A.J. has performed consulting activities for Kite/Gilead, Novartis, BMS/Celgene, Bluebird Bio, Epizyme, Lonza, Ipsen, and Instill Bio. E.P.D. declares no competing financial interests. ■

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MYELOID NEOPLASIA

Comment on Zhang et al, page 359

The 2 faces of ERK2 in MPNs

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In this issue of *Blood*, Zhang et al[1] reported that extracellular signal-regulated kinase 2 (ERK2) substrate-binding domains have opposing roles in Janus kinase 2 V617F (*JAK2*V617F)-driven myeloproliferative neoplasms (MPNs). One of the domains, ERK2-docking (ERK2-D), may be a promising therapeutic target for MPNs. Conversely, the other domain, ERK2-DEF–binding pocket (ERK2-DBP), blocks progression of the disease in a mouse model. This changes the perception that simply inhibiting the catalytic activity of ERK1/2 in MPNs would be an effective therapeutic strategy.

MPNs are chronic disorders, and patients present with symptoms that affect their quality of life and have a significant risk of thrombotic complications, fibrotic evolution, and leukemic transformation.[2] There is a real need to improve the understanding of MPN biology and develop new combinations of targeted therapies to eradicate the MPN clone by shutting off all the activated pathways in the MPN cells.

MPNs are hematopoietic stem cell diseases characterized by clonal expansion of 1 or more myeloid lineages resulting in erythrocytosis (polycythemia vera [PV]), in thrombocytosis (essential thrombocythemia [ET]), or in progressive fibrosis in the bone marrow (primary and post PV/ET myelofibrosis [MF]). All these chronic states of disease can evolve into highly aggressive acute myeloid leukemia with poor survival. MPNs are driven by a mutation of 1 of the 3 driver genes—Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia virus (*MPL*).[2] The resulting constitutive activation of JAK2 signaling activates STAT, PI3K/AKT, and MEK/ERK signaling.[2]

JAK2 inhibitors are now used for the treatment of MF and PV with clinical benefits such as a decrease in inflammatory symptoms and splenomegaly. However, unlike imatinib and other kinase inhibitors in *BCR-ABL*–driven chronic myeloid leukemia, JAK2 inhibitors do not significantly decrease the MPN clone, and MPN cells can survive and proliferate when treated with JAK2 inhibitor monotherapy.[3] Several experimental approaches have shown that activation of mitogen-activated protein kinase (MAPK) pathway signaling (MEK/ERK) contributes to the JAK2 inhibitor persistence or resistance in MPNs.[4,5]

ERK1/2 are terminal serine/threonine kinases of the MAPK signaling pathway that act on multiple downstream targets involved in cellular proliferation and survival. In mouse models of MPNs, ERK1/2 deficiency reduced the frequency of *JAK2*V617F clones and decreased the features of MPNs.[6] Combining the JAK2 inhibitor ruxolitinib with ERK inhibitors normalized erythrocytosis and splenomegaly in mice with *JAK2*V617F MPNs with an interesting long-term clone reduction.[6]

ERK2 interacts with substrates through 2 domains on opposing faces of the protein (see figure). The D domain binds Leu-X-Leu or hydrophobic sequences proximal to basic residues,[7] and the DBP domain (docking site for ERK and FXF [DEF]–DBP) binds sequences that exhibit Phe-X-Phe followed by a Pro residue.[8]

To understand the roles of ERK2 substrate-binding domains in MPN pathogenesis, Zhang et al generated an ERK2-mutant knockin mouse model with an inactivated ERK2-DBP domain but with preserved ERK2 kinase activity and D domain function. Wild-type (WT) mice developed an expansion of the immature erythroid compartment with splenomegaly. *JAK2*V617F was transduced into the bone marrow stem and progenitor cells that expressed ERK2-DBP mutant, ERK2-WT, or ERK2 knockout. When transduced cells were transplanted into sublethally irradiated immunodeficient mice, ERK2-DBP–mutant recipients developed PV and rapidly progressed to MF at 12 weeks.

The mechanism that explained this unexpected effect, which involved the 3 myeloid lineages instead of the predicted lineage was explored in vitro. Although