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CLINICAL TRIALS AND OBSERVATIONS

Comment on Etra et al, page 481

Progress in risk-adapted acute GVHD therapy

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In this issue of *Blood*, Etra et al report that itacitinib, a selective JAK1 inhibitor, has activity as the primary treatment of acute graft-versus-host disease (GVHD). The use of itacitinib spared steroid exposure and was associated with decreased infectious complications compared with a matched control population.[1]

Advances are needed to improve the safety and efficacy of acute GVHD treatment. Systemic corticosteroids (commonly, prednisone at 1 to 2 mg/kg/day starting dose) are the long-standing standard initial therapy for acute GVHD. Limitations of this practice include incomplete efficacy with subsequent steroid-refractory GVHD and associated mortality, morbidity, and complications of prolonged steroid therapy. As important, the universal application of high-intensity treatment does not respect individual disease risk. Important prior research has defined clinically based and biomarker-based tools to provide risk stratification of acute GVHD,[2,3] and the field has begun to test novel interventions in acute GVHD risk subgroups. These new strategies may hold promise to personalize GVHD therapy, in which the right intensity of therapy is delivered to the right patient.

In this current report, the investigators describe notable results of a multicenter phase 2 trial testing steroid-free initial therapy with itacitinib among patients with clinical and biomarker-defined low-risk acute GVHD. Although ruxolitinib has been studied in steroid-refractory acute GVHD (and is now approved for this indication),[4] the investigators chose to test itacitinib in this setting for potential advantage in hematologic toxicities. As well, itacitinib has been tested in combination with corticosteroids for acute GVHD treatment.[5] A total of 70 patients with low-risk (Minnesota standard risk, biomarker AA score 1) acute GVHD were treated with itacitinib and compared with a matched control population (140 patients from a prospectively assembled multicenter consortium) meeting the same eligibility criteria and treated with at least 0.5 mg/kg/day prednisone therapy. The results support that this steroid-free therapy achieved a high response rate (overall response rate [ORR] of 89% at day 28). There was no signal of inferior outcomes compared with the steroid control group considering day 28 ORR, response according to subgroups of GVHD organ involvement and severity, time to initial response, durability of response, or risk for treatment failure or GVHD flare. Importantly, the itacitinib-treated participants had significant reduction in cumulative prednisone exposure through days 28 and 56 of therapy compared with control participants and significant reduction in risk of infectious complications. Itacitinib discontinuation occurred for lack of efficacy (10% of participants), treatment-emergent (most commonly hematologic) adverse events (AEs) (29%), or relapse of malignancy (3%). A total of 30% of itacitinib-treated participants had other (nonhematologic, noninfectious) treatment-emergent ≥ grade 3 AEs, with the highest frequency events being alanine aminotransferase increase and hypertension. There was no evidence of worsened long-term outcomes, including chronic GVHD, relapse, and nonrelapse mortality. Potential limitations (nonrandomized control group, not standardized infectious prophylaxis, limitation to AA biomarker score 1 participants, possibility that topical therapy alone could be sufficient) of this work were well described.

Additional progress in the field will require selection of priority interventions and allied trial designs for risk-adapted therapy. A national Blood and Marrow Transplant Clinical Trials Network randomized trial is currently underway in high-risk acute GVHD (NCT04167514). For lower-risk acute GVHD (the majority of acute GVHD cases), at least 3 (lower-dose prednisone,[6] sirolimus,[7] itacitinib) steroid-minimizing or steroid-free primary

therapy approaches have now been tested, albeit with variation in the definition of standard or lower-risk acute GVHD. These and other agents should be considered in development of randomized trials, and such investigation should capture a full extent of treatment benefit and risks, including steroid exposure, infectious complications, and patient-reported outcome measures. Taken together, there is significant promise to advance the field toward personalized therapy of acute GVHD.

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LYMPHOID NEOPLASIA

Comment on Cappelli et al, page 503

Newer insights on how to TEC down T-ALL

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In this issue of *Blood*, Cappelli et al[1] investigated the interplay between T-cell acute lymphoblastic leukemia (T-ALL) and endothelial cells (ECs) with the hypothesis that the tumor microenvironment (TME), especially ECs, may affect drug responses.

T-ALL is an aggressive and often incurable disease which is treated with a similar chemotherapeutic backbone as used for B-cell ALL. Unlike B-cell ALL, there has not been an explosion of novel therapies for T-ALL. This is especially concerning for early T-cell precursor (ETP) ALL, which has significantly worse outcome. The options for salvage are limited, mainly conventional chemotherapy and hematopoietic stem cell transplantation (HSCT). Nelarabine (compete response rates: 30% to 40%) has enabled some patients with relapsed/refractory T-ALL to undergo HSCT and achieve long-term survival.[2]

The TME has a significant influence on cancer development and progression. It is well established that cancer pathogenesis involves genomically transformed cancer cells interacting with and benefiting from recruited accessory cells in the TME.[3,4] In particular, fibroblastic, endothelial, and other stromal cell components are driving forces in tumor development.[3,4] In the TME host-leukemia interaction, there is a vulnerability that can be exploited to develop personalized treatments. As major gatekeepers of cellular transmigration, ECs profoundly impact tumor angiogenesis and even peripheral immune cell trafficking into tumor compartments. The investigators used a nontransformed serum/xenobiotic free EC platform called E4ORF1[5] which allows studying leukemia-host interactions while maintaining their angiogenic potential. First, by performing a drug screen, they identified T-ALL liabilities using 22 patient-derived xenograft (PDX) models in vitro and in vivo. They then performed coculture experiments and generated bulk and single-cell RNAseq gene set enrichment analyses and hierarchical clustering and pathway analysis. Tumor-associated endothelial cells (TECs) have been shown to modulate T-ALL aggressiveness via multiple synergistic mechanisms, including SDF1α/CXCR4, DLL4JAG1-2/NOTCH, and IGFBP7/IGF1 prosurvival pathways. It has been known that therapies targeting the host endothelial cells impact the clinical responses and the potential side effects[6] (the Endothelial Activation and Stress Index score in cellular therapy). Additionally, their significance motivates therapeutic targeting of TECs via pharmacological or immunologic approaches. Identifying EC-associated molecular pathways and alterations may enable the development of novel therapeutic targets to evade TEC-mediated chemotherapeutic resistance and to enhance the efficacy of already established agents. Using high throughput screening of 433 compounds from clinically active and US Food and Drug Administration–approved agents, the investigators performed experiments focusing on signaling pathways, epigenetic changes, and anti-apoptotic pathways. Redundancy testing using multiple drugs targeting the same pathways was used to confirm the results. A subset of these agents was examined in vitro, whereas others, including irinotecan, ruxolitinib, tofacitinib, bortezomib, panabinostat, daunorubicin, and OSI906 (linsitinib), were tested in vivo using T-ALL PDX. They found that the TECs were able to sustain T-ALL in stress conditions and counteracted the antiapoptotic effects of several drugs. Furthermore, TEC and T-ALL remained engaged at the genomic level undergoing reciprocal transcriptomic changes. At the single-cell resolution, this was characterized as "education signatures" associated with the bidirectional enhancement of canonical pathways (T-ALL: JAK-STAT, MAPK, TGFB, EGFR, NOTCH, and, MYC; TEC: JAK-STAT, NF-κB, TNFα, and VEGF); up-/downregulation of genes driving multiple pathogenetic processes