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CLINICAL TRIALS AND OBSERVATIONS

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Ruxolitinib for steroid-resistant acute GVHD

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In this issue of *Blood*, Jagasia et al report the results of a phase 2 study investigating ruxolitinib for the treatment of steroid-refractory acute graft-versus-host disease (GVHD).[1]

Acute GVHD remains a most fickle complication of hematopoietic stem cell transplantation (HSCT),[2] ultimately preventing broader application of HSCT. Different strategies of immunosuppression have resulted in a reduced risk of acute GVHD both in HLA-matched and mismatched HSCT and reflected in improved nonrelapse mortality (NRM).[3] Nevertheless, once acute GVHD develops, it still negatively impacts patient outcome. Actual treatment of GVHD treatment has not improved in the last few decades.[2,4] The standard treatment of acute GVHD is based on systemic, 1 or 2 mg/kg steroids, which may result in sustained response in ≤60% of patients. However, despite many studies, no agents for treatment of glucocorticoid-resistant or refractory GVHD have clearly emerged as a gold standard, and treatment options remain limited,[2-4] with a dismal outcome for these patients.[5] Treatment of steroid-resistant acute GVHD thus remains in 2020 an unmet clinical need.

In this study, the JAK1/2 inhibitor ruxolitinib was investigated in a prospective, multicenter, open-label phase 2 study that enrolled 71 patients with steroid-refractory acute GVHD (progression after 3 days or lack of improvement after 7 days of systemic ≥2 mg/kg steroids).[1] The overall response rate at day 28 (primary end point of the study) was 54.9%, with a substantial proportion of complete responses (26.8%). Responses were seen irrespective of the affected site (even if actual rates may suggest that sensitivity to ruxolitinib decreases from skin to gastrointestinal tract to liver), with a significantly higher chance of response in grade II versus grade III-IV GVHD. The safety profile of ruxolitinib treatment was acceptable, with cytopenias (likely related to the treatment) and infectious complications the most significant complications. The 1-year overall survival was 42.6% for all patients, with statistically significant differences between responders and nonresponders to ruxolitinib (66.2% overall survival at 1 year for responding patients at day 28 vs only 10% in nonresponders). With the caveat of limited follow-up, responses seem sustained with limited rates of evolution to chronic GVHD, even with discontinuation of ruxolitinib and meaningful tapering of steroids.

A number of new immunosuppressive or immunomodulatory agents have been developed in the past few years for different autoimmune diseases, but none has been proven effective in steroid-refractory GVHD. Several drugs have been shown effective in small series, such as monoclonal antibody–depleting lymphocyte (eg, antithymocyte globulin [ATG] and alemtuzumab) or interfering with their function (eg, daclizumab), as well as anti-cytokine agents (eg, infliximab and etanercept), but they all failed when challenged in prospective phase 2 or phase 3 trials (eg, ATG, ABX-CBL, and inolimumab).[4] In retrospective analysis, the best results are still seen with extracorporeal photopheresis, or with mycophenolate and mTOR inhibitors. More recently, promising data have been reported with mesenchymal stem cells, vedolizumab, anti-CD3/CD7 immunotoxin, α1 anti-trypsin, brentuximab vedotin, and the anti-CD26 begelomab, in addition to ruxolitinib.[6]

Jagasia et al convincingly demonstrate that ruxolitinib may rescue approximately half of patients with steroid-refractory acute GVHD: 1-year NRM was 28% in patients with sustained response. This remarkable effect on NRM was retained even in patients with grade III-IV GVHD, provided that they achieved complete or very good partial response at day 28. In this severe disease group, 1-year NRM was 9.1%. On the other hand, a substantial proportion of patients had limited benefit from ruxolitinib treatment, showing no clinical response and very bad outcome. While this study also confirms that response at day 28 is an excellent end point for clinical trials on GVHD,[7] it also highlights the need for pretreatment or early prognostic factors that identify patients who are unlikely to benefit from ruxolitinib. In this study, clinical response to ruxolitinib was associated with increased baseline ST2 and TNFR1, but not REG3A and trappin-2/elafin.[1] Further studies are needed to confirm these observations and possibly to correlate these findings with mechanistic interpretations. It is not clear whether biomarkers associated with GVHD simply reflect the extent and the aggressiveness of GVHD (as do other clinical factors, such as global grading and duration of steroid treatment) or may also suggest specific mechanisms of damage that may play a role in GHVD pathophysiology.[2] For instance, ST2 has been extensively associated with not only GVHD[8] but also transplant-associated microangiopathies (TA-TMAs) and broader endothelial damage.[9] It has been recently shown that in TA-TMA associated with GVHD, the initial endothelial injury may activate complement through the generation of neutrophil extracellular nets (as demonstrated using circulating double-stranded DNA), eventually linking GVHD,

endothelial damage, complement activation, and TA-TMA.[10] These findings may suggest that in some forms of GVHD, additional mechanisms of damage are triggered, which are only partially defused by "standard" immunosuppressive agents, possibly accounting for poor response to not only steroids but also other "conventional" second-line agents. This broad derangement of both adaptive and innate immunity (including inflammation) is embedded in GVHD and its pathophysiology and largely contributes (together with steroids and other anti-GVHD therapies) to complications associated with GVHD, such as life-threatening infections. This observation reconciles with the disappointing findings from previous trials showing that the effect on GVHD per se is necessary, but not sufficient, to improve the long-term outcome of patients with steroid-refractory GVHD.

In summary, this phase 2 study identifies ruxolitinib as an effective agent for the treatment of steroid-refractory acute GVHD, which hopefully will be confirm by the ongoing phase 3 randomized trial (REACH2 study). More study is still required to better understand the biological mechanisms underlying the lack of response in a substantial proportion of patients. The treatment of acute GVHD has remained disappointing for decades; ruxolitinib and a few other agents seem to finally offer better therapeutic options. We still have a long road ahead, but the path toward more effective management of acute GVHD and possibly a better understanding of the underlying mechanisms is on the way.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Lacy et al, page 1759

DLBCL subclassification: divide and conquer?

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In this issue of *Blood*, Lacy et al contribute to overhauling the molecular classification system for diffuse large B-cell lymphoma (DLBCL).[1] Two decades ago, gene expression profiling (GEP) enabled the division of DLBCL into 2 cell-of-origin (COO) molecular subgroups, a stratification with prognostic implications (see figure).[2] This stimulated the search for therapies that could exploit the unique molecular features underlying each subgroup, long before the concept of "precision medicine" had gained popularity. The eventual failure of numerous clinical trials of targeted therapies selecting patients using COO implies that this classification, although foundational, lacks sufficient granularity to serve this purpose.

Over the last decade, large sequencing efforts have yielded a compendium of genetic aberrations common in DLBCL, with many of these exhibiting segregation by COO.[3,4] Although this lends credence to molecular differences underlying the subgroups, the heterogeneity implied a hierarchy of genetically distinct entities. In 2018, two studies proposed a completely new framework for DLBCL subclassification relying on tumor genetics.[5,6] They each suggested that DLBCL can be divided into at least 4 genetic clusters with some of these strongly enriched for cases representing either COO subgroup (see figure). Although broadly consistent in their conclusions, there were also significant discrepancies, leaving the nature of the DLBCL genetic subgroups unresolved.

The study by Lacy et al affirms the biological validity of 3 of the previously postulated clusters (see figure) and highlights methodological differences that likely underlie discrepancies between genetic classifications. They applied a distinct clustering method to mutation and sparse copy number data from 928 patients, mainly representing cases of de novo DLBCL and identified 6 clusters, which they named according to the most prevalent genetic feature(s) (see figure). As had been shown previously, primary central nervous system lymphomas were mostly assigned to a cluster typified by *MYD88* mutations. Based on genetic features shared with marginal zone lymphoma, the second cluster may represent cases of occult transformation. Similarly, the third cluster contains many of the transformed follicular lymphoma cases and is enriched