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significantly improved outcomes, no plateaus in PFS have been observed. Moreover, the response rate depends on treatment modality and schedule. For example, the addition of obinutuzumab to ibrutinib induced uMRD in 20% to 60% of patients, which is significantly higher than the outcome obtained with IR (below 10% of patients, when all known precautions for cross-trial comparisons were applied).[7] Importantly, other targeted therapies, such as venetoclax (a selective inhibitor of BCL2), induced profound clinical remissions with uMRD in a high proportion of patients across all risk groups. Also, combinations of targeted therapies (eg, venetoclax+ibrutinib+anti-CD20 monoclonal antibodies) have improved the proportion and quality of remissions (including uMRD), with a very long PFS.[8,9] If confirmed, these data would reinforce rather than invalidate the "uMRD paradigm."

Finally, to clarify the role of MRD in CLL management requires international collaboration that should include the US Food and Drug Administration and the European Medicines Agency as central partners. Meanwhile, the recommendation formulated by the International Workshop on CLL that MRD-guided therapy should be restricted to clinical trials remains sound.[10]

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

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LYMPHOID NEOPLASIA

Comment on Moskowitz et al, page 2828

JAK/STAT: a pathway through the maze of PTCL?

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In this issue of *Blood*, Moskowitz et al[1] report the result of treatment with ruxolitinib for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL), demonstrating that the JAK/STAT pathway is clinically relevant in T-cell lymphoma.

In the hematology-oncology community, few would argue that some of the biggest therapeutic disappointments in lymphoid malignancies are seen in non–mycosis fungoides PTCL. The reasons for our slow advancement in this area are many, including the rarity of these disorders, their extreme heterogeneity, and their geographic diversity. In the 2017 World Health Organization Classification, there are least 29 different subtypes of PTCL; each a relative challenge to pathologically categorize and each a unique entity.[2]

We are, however, making progress through this maze of PTCL, moving away from combination chemotherapy regimens that have been borrowed from the B-cell lymphomas, like cyclophosphamide, doxorubicin, vincristine, prednisone and ifosfamide, carboplatin, etoposide, toward lineage-specific chemotherapy, such as pralatrexate. We are now using in the front line a drug that targets an antigen, CD30, found to a variable degree on PTCL, with improvement in therapeutic outcome. We use therapies that rely on T-cell lymphoma's unique vulnerability to epigenetic disruption, such as the histone deacetylase inhibitors and hypomethylating agents. In doing so, we are made aware that the treatment of PTCL certainly needs to be lineage specific and will likely become more subtype specific. There is not a "one-size-fits-all" for PTCL. Only some subtypes of PTCL have CD30 overexpression and/or recurrent mutations in genes that govern the epigenome. Certainly, making our way through this maze will not and has not been simple and will require learning more about the malignant T cell and its vulnerabilities.

Signaling through JAK1 and/or JAK2 within the tumor or its microenvironment has been commonly reported in PTCL.[3] Given the high rate of refractory and relapsed disease, and the need for more efficacious therapy, Moskowitz et al conducted a biomarker-driven study of ruxolitinib for the treatment of patients with relapsed/refractory PTCL in this multicenter, investigator-initiated, phase 2 trial (#NCT02974647). Ruxolitinib, an oral agent, is a JAK1/2 inhibitor. Fifty-two evaluable patients with a variety of PTCLs were treated with ruxolitinib 20 mg orally twice daily until either progressive disease or unacceptable toxicity. Assessments for

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response were performed after 56 and 140 days of therapy and then every 84 days. The primary endpoint of the study was assessment of clinical benefit rate (CBR), defined as complete and partial responses, or stable disease that lasted at least 6 months.

Patients were assigned and evaluated in 3 cohorts: cohort 1 included those with known activating JAK and/or STAT mutations; cohort 2 included those with functional activation of JAK/STAT by demonstration of ≥30% pSTAT3 3 expression in tumor cells by immunohistochemistry; and cohort 3, which those with neither genetic or phenotypic evidence of JAK/STAT activation or insufficient tissue for this assessment. Ruxolitinib activity was found to be greater in those patients with PTCL with JAK/STAT activating mutations or active signaling, with cohort 1 having a CBR of 53%; cohort 2 having a CRB of 45%; and cohort 3 having a CRB of 13%. The median time to best response was 6.3 months. Adverse events were consistent with known side effects of this drug and primarily involved cytopenias.

Although an overall CBR of 35% is likely commensurate (although many may agree it is also commiserate) with other approved agents, 8 exceptional responders were identified with responses >1 year. These included 4 of the 5 patients with T-large granular lymphocytosis (T-LGL), the CBR of which was 80%. Of the 8 patients with T-prolymphocytic leukemia (T-PLL), CBR was 50%, all in patients with evidence of JAK/STAT activation. In contrast, only 1 of 7 patients with mycosis fungoides experienced a response to this treatment.

From this study, we learned that an already available oral JAK inhibitor was active against various subtypes of PTCL with acceptable toxicity most often when JAK/STAT pathway activation could be demonstrated. Although lack of JAK/STAT activation appears to predict a reduced response to ruxolitinib in PTCL, the presence of activation was not a guarantee of response, and the lack of activation did not assure there would be no response. This was clearly demonstrated in some cases of T-LGL.

The responses seen in the small number of patients with T-PLL and T-LGL are particularly encouraging. Here, we have 2 T-lymphocytic entities characterized by circulation of malignant cells, cytopenias, and splenomegaly. T-PLL is an aggressive disorder with very limited treatment options. T-LGL is an indolent disorder with treatment options that are successful in approximately half of cases. Of interest, in T-PLL, up to 76% of cases have mutations in JAK1, 2, or 3 or STAT3 or 5B; in LGL, up to 40% of cases have mutations. Although 60% of the patients with LGL are symptomatic, STAT3 mutations have been associated with increased symptoms and shorter time to treatment failure.[4-7]

We look forward to studies that would specifically address these 2 neglected subtypes of PTCL with either expansion of single-agent investigation and/or combination with other pathway inhibitors, such as bcl-2 inhibitors or Pi3 kinase inhibitors. We also anticipate further characterization of the role that JAK/STAT inhibition may play in the treatment of the larger group of patients diagnosed with non–mycosis fungoides PTCL who need improved outcomes.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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MYELOID NEOPLASIA

Comment on Sheng et al, page 2838

Ticket to divide: m^{6}A reader YTHDC1 drives acute myeloid leukemia proliferation

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In this issue of *Blood*, Sheng et al show that the N^6-methyladenosine (m^{6}A) messenger RNA (mRNA) reader protein YTH domain containing 1 (YTHDC1) promotes leukemic cell proliferation through stabilizing transcriptions of DNA replication initiation complex subunit MCM4.[1]

The central dogma of biology is that DNA is transcribed to RNA, which is then translated into protein. Each step of the process is highly regulated by discrete modifications to the target molecule and associated factors. These modifications impart changes in the target molecule so profound to its function that related mutations account for most oncogenic drivers. The field of cell biology has been broadly focused on two-thirds (DNA and protein) of the central dogma trifecta. We still need to understand how modifications to RNA contribute to disease and development.

RNA modifications affect the stability, localization, and translation efficiency of the molecule. The m^{6}A modification cooccurs with transcription and occurs within a DRACH (A/G/U; G/A; A; C; A/C/U) consensus sequence.[2] Broadly speaking, the

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