Comment on Song et al, page 3148

A cauldron of choices

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In this issue of *Blood*, Song et al[1] report long-term follow-up of a phase 2 study investigating the second-generation Bruton tyrosine kinase inhibitor (BTKi) zanubrutinib in 86 patients with relapsed mantle cell lymphoma (MCL) and demonstrate the continued efficacy and favorable safety profile across most prognostic subtypes. The authors also assess the mutation status of nearly two-thirds of patients by next-generation sequencing to further explore the molecular underpinnings associated with depth of response.

Outcomes of relapsed/refractory (R/R) MCL have significantly improved because of the advent of novel therapeutics.[2] The initial leap occurred with BTKi, which targeted the major Achilles heel of this incurable subtype of lymphoma. The excellent efficacy and manageable safety results led to the Food and Drug Administration (FDA) approval of the first-generation irreversible BTKi ibrutinib for R/R MCL.[3] More selective BTKi's like acalabrutinib and zanubrutinib[3] were subsequently approved by the FDA. Although the overall efficacy of second-generation BTKi's appear to be similar with a more favorable toxicity profile compared with ibrutinib, follow-up on this class of inhibitors has been short. Thus, several questions about durability, long-term tolerability, and predictors of response have lingered.

In the Song et al study with a median follow-up of 35.3 months, zanubrutinib showed excellent efficacy with an overall response rate (ORR) of 83.7%, complete response rate (CR) of 77.9% with a median progression-free survival (PFS) at a notable 33 months. The median duration of response was not reached (NR), and the depth of response was associated with PFS and overall survival (OS). The median PFS was NR in patients achieving a CR vs 16.6 months in patients achieving less than a CR. The PFS was expectedly prolonged for low-risk subgroups of patients with low-/intermediate-risk MIPI (Mantle Cell Lymphoma International Prognostic Index), Ki67 index <30%, 1 prior line of therapy, and TP53 wild-type. Although limited by small numbers, it was interesting to note that the response duration and PFS were similar in high-risk subgroups of patients with bulky, refractory disease and blastoid histology. The longer-term follow-up of adverse events (AEs) did not demonstrate new safety signals or new deaths owing to AEs with the overall frequency of any grade or grade ≥3 AEs of interest decreased over time. Higher-grade infections were reported in 18.6% of patients; on the other hand, there were no reported cases of atrial arrythmias, higher-grade cardiac AEs, or second primary malignancies.

This study also explored questions that have clinical implications in the management of R/R MCL. Fifty-four patient samples were assessed via next-gene sequencing to understand the association between mutations and response. Although limited by a small sample size, patients with disease progression as best ORR had higher mutation rates of NOTCH1, TP53, and BCL10/CARD11 and shorter PFS compared with nonprogressing patients. These findings are consistent with other studies[4] and underscore the unmet need to investigate novel treatments in patients with MCL enriched for these mutations.

The other notable result of this study was the assessment of outcomes in patients who progressed on zanubrutinib. The median OS among the 37 patients with disease progression was 15.7 months at a median follow-up of 11.3 months. These are relatively encouraging data because prior studies[5] demonstrated extremely poor outcomes in post-BTKi failures with median OS under 6 months.

Thus, a burning question of which BTKi should be considered in patients with R/R MCL remains a point of scrutiny and ongoing debate. There are no prospective trials in R/R MCL comparing first- to second-generation BTKi. Two recent head-to-head randomized phase 3 trials comparing ibrutinib with zanubrutinib in Waldenstrom macroglobulinemia[6] and R/R chronic lymphocytic leukemia[7] demonstrated comparable efficacy; however, zanubrutinib demonstrated a more favorable AE profile as compared with ibrutinib. The long-term efficacy results of the 3 single-arm prospective trials are summarized across the 3 FDA-approved BTKi in R/R MCL (see table). Being mindful of limitations across these studies, such as differences in baseline demographic and disease characteristics, computed tomography– vs positron emission tomography–based response assessment, it appears that the efficacy may be similar for the 3 agents, although survival data may appear to be better with

Table 1. Efficacy results of FDA-approved first- and second-generation BTK inhibitors

BTKi	N	Median lines of prior treatments (range)	ORR, %	CR, %	Median follow-up (mo)	Median duration of response (mo)	Median PFS (mo)	Median OS (mo)
Ibrutinib[3]	111	3 (1-5)	67	23	26.7	17.5	13	22.5
Acalabrutinib[10]	124	2 (1-5)	81	48	38.1	28.6	22	NR
Zanubrutinib[1]	86	2 (1-4)	83	77.9	35.3	NR	33	NR

second-generation BTKi's. Despite this, it is evident that BTKi treatment is not curative, and additional treatments are needed. Hence, a close review of the AE profile may assist with the appropriate BTKi selection. The second-generation BTKi's have a more favorable cardiac and bleeding AE profile compared with ibrutinib. Low-grade AEs like arthralgia and myalgias are seen with ibrutinib and acalabrutinib, whereas caffeine-responsive headaches are more common with acalabrutinib. Finally, dosing schedule (daily vs twice a day) and drug-drug interactions may also dictate the choice between second-generation BTKi's.

The treatment landscape of MCL continues to evolve at an accelerated pace. Clinical trials investigating but not limited to chimeric antigen receptor therapy (brexucabtagene autoleucel)[8] and reversible BTKi's like pirtobrutinib[9] have shown promising efficacy and safety in R/R MCL, including patients with hard-to-treat subgroups like blastoid, refractory, TP53 mutation, and prior BTK failures. In addition, we await results from clinical trials exploring BTKi's earlier in the treatment course. The future of R/R MCL looks bright, although much work remains to be accomplished in high-risk subgroups. Even though it may appear that there is a cauldron of choices, appropriate patient selection remains key. The choices we make will determine the future of our patients.

As J. K. Rowling aptly said, "It is our choices, Harry, that show what we truly are far more than our abilities."

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PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Comment on Sprenkeler et al, page 3166

Actin powers the neutrophil traps

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In this issue of *Blood*, Sprenkeler et al[1] demonstrate that actin polymerization is essential for the formation of neutrophil extracellular traps (NETs). The actin cytoskeleton powers a myriad of cellular processes in eukaryotic cells. In no other cell type is actin more relevant than in neutrophils. These essential phagocytes rapidly mobilize to sites of infection to capture and kill pathogens. Over their lifespan, neutrophils must leave the bone marrow, revert to a quiescent state in the circulation, polarize once again to invade tissues, and hunt small microbes or stretch to great lengths to tackle large microbes. As a testament to the potent actin dynamics under the hood, neutrophils move faster than any other human cell and can wield particles many times their size. Eventually, most neutrophils depolarize and die or journey to other distal sites. This complex lifestyle relies on robust actin dynamics and their precise spatiotemporal regulation. However, whether and how actin influences the release of NETs, one of the neutrophil's most unique cell biological feats, remained incompletely understood.

NETs are decondensed extracellular chromatin structures deployed by neutrophils to combat pathogens but also contribute to pathology. NET release occurs primarily via a cell death process termed NETosis that progresses through the disassembly of the nuclear envelope, cell lysis, and chromatin decondensation of epic proportions. Chromatin posttranslational modifications, such as histone citrullination, are implicated in chromatin decondensation as well as the translocation of the protease neutrophil elastase (NE) from the azurophilic granules to the nucleus, where it partially cleaves histones to disrupt nucleosome organization.[2] The release of NE from granules is triggered by reactive oxygen species (ROS) via the dissociation from the membrane-associated azurosome complex and inflammasome-dependent gasdermin D activation.[3,4] In the cytosol, NE interacts with and degrades the actin cytoskeleton, driving cell depolarization, facilitating cell lysis,