Pirtobrutinib: the 'brute' with a softer side

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In this issue of *Haematologica*, Shah and colleagues report toxicity and outcomes of a subgroup of 127/597 patients with low-grade B-cell lymphomas, previously intolerant to at least one Bruton tyrosine kinase inhibitor (BTKi) and without progressive disease (PD), who were treated with pirtobrutinib in the phase I/II BRUIN study.[1] This subgroup analysis provides clinically relevant data because up to 40% of patients receiving covalent BTKi will discontinue treatment despite ongoing clinical efficacy because of adverse events (AE). Such AE include atrial fibrillation, bleeding, infections, diarrhea, rash, and arthralgias,[2] most of which are due to binding of the BTKi to off-target kinases like EGFR, SRC, and TEC.[3] Pirtobrutinib, in contrast to ibrutinib and other covalent BTKi, is a non-covalent BTKi with a >100-fold selectivity for BTK compared to 363/370 (98%) other kinases tested *in vitro*, limiting the potential for off-target toxicities.[4] As proof of principle, pirtobrutinib was associated with very low (<5%) discontinuation rates from drug-related AE in previously published BRUIN cohorts of patients with relapsed / refractory chronic lymphocytic leukemia (CLL) / small cell lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL).[5,6]

In the study by Shah and colleagues, 94% of patients had previously received ibrutinib at some point in their disease course.[1] The most common adverse events leading to ibrutinib discontinuation were cardiac disorders (32%), infections (10%), neutropenia (9%), rash (9%), arthralgias / myalgias (8%), bleeding / hemorrhage (7%), gastrointestinal disorders (6%), fatigue (5%), and pain (5%), which is consistent with other studies of ibrutinib in CLL/SLL.[7,8] A total of 64% of the treatment-emergent AE that led to discontinuation of a prior BTKi did not reoccur with pirtobrutinib, except for infections, neutropenia, and gastrointestinal disorders, all with recurrence rates >50%, although these tended to be low grade with only 2 patients discontinuing the drug due to infection or neutropenia.

Half of the infections on pirtobrutinib were COVID-related, as most of the study was conducted during the COVID-19 pandemic. This highlights the importance of preventative measures such as vaccination and consideration of immunoglobulin replacement therapy in patients with hypogammaglobulinemia. Despite this, no patients in BRUIN discontinued pirtobrutinib because of a recurrent infection, suggesting it is a safe option in this patient population known to have dysfunctional humoral and cellular immunity. Of particular importance, 75% patients with a prior cardiac event had no recurrence of this complication and no patient discontinued pirtobrutinib for the same AE that led to prior BTKi discontinuation. In addition to being better tolerated than what would have been expected with a switch to a different covalent BTKi, pirtobrutinib was also effective in this subgroup with an overall response rate of 77% in CLL/SLL (74% partial response [PR], 3% PR with lymphocytosis) and 81% (43% complete response [CR] and 38% PR) in MCL.[1] High response rates are anticipated as no patient had previously discontinued BTKi for PD.

Even though in the study by Shah and colleagues prior exposure to acalabrutinib or zanubrutinib was limited (9%), results can still be generalized to patients intolerant to second-generation BTKi. First, these patients are expected to experience more, not less, toxicity with a switch to ibrutinib. Second, among patients who received acalabrutinib or zanubrutinib after ibrutinib intolerance, 17% and 7% discontinued therapy due to AE, respectively.[9,10] Even though these discontinuation rates are close to the 10% discontinuation rate due to AE reported in this subgroup of BRUIN,[1] significantly greater clinical efficacy is expected with pirtobrutinib.

Of note, 15% of patients included in the study by Shah and colleagues had taken and discontinued a prior BTKi as part of a combination regimen.[1] The attribution of toxicity to individual agents leading to the discontinuation of that particular line of therapy before enrollment in the BRUIN trial was not collected. If the toxicity was related to another agent such as chemotherapy or a CD20 monoclonal antibody instead of the prior BTKi, this could have increased the likelihood of tolerating pirtobrutinib and, therefore, of underestimating the incidence of reported recurrent tox-

icities. However, given that most combination therapies included a continuous BTKi with a fixed number of cycles of the other agent(s), it is likely that the previously reported AE were truly related to the BTKi.

Overall, the findings from the analysis by Shah and colleagues support the use of pirtobrutinib in patients with low-grade B-cell lymphomas who have previously discontinued a different BTKi due to intolerance but without PD. The drug's improved tolerability profile, coupled with its sustained efficacy, reinforces its position as a fearsome player in the B-cell lymphoma arena. This 'brute' with a softer side is an excellent option for patients who experienced toxicities on a covalent BTKi, although 25-30% patients will discontinue pirtobrutinib due to PD, highlighting the need for novel therapies.

Disclosures

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Contributions

JD and DV wrote the manuscript.

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