High-risk stays high-risk: Bruton tyrosine kinase inhibitors in B-cell malignancies

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In this issue of *Haematologica*, Xu *et al.* present an overview of the genomic landscape of patients with B-cell malignancies who received the Bruton tyrosine kinase (BTK) inhibitor zanubrutinib after prior intolerance to ibrutinib and/or acalabrutinib.[1] Based on a 106-gene targeted next-generation sequencing panel, they characterized baseline and relapse samples from 71 patients with relapsed/refractory B-cell malignancies. In line with previous reports on relapsed/refractory B-cell malignancies, a high rate of mutations in genes such as *TP53*, *SF3B1* and *ATM* was observed prior to the start of zanubrutinib. Patients with these alterations had a shorter progression-free survival under zanubrutinib therapy than patients without these alterations. The authors also looked at the incidence and impact of *BTK* and *PLCG2* mutations, which are known contributors to treatment resistance, particularly in the context of chronic lymphocytic leukemia. Three patients had *BTK* C481S mutations at different variant allele frequencies prior to starting zanubrutinib and had relatively short responses. Of nine patients with progression while receiving treatment with zanubrutinib, four had *BTK* C481S mutations, mostly accompanied by *PLCG2* mutations. Overall, the authors concluded that the mutational landscape and particularly its prognostic relevance in terms of response and duration of response are important in the context of BTK inhibitors. The study contained a particular cohort of patients with intolerance to ibrutinib and/or acalabrutinib, who constitute up to 40% of patients with relapsed/refractory chronic lymphocytic leukemia.[2] Given the availability of several covalent and non-covalent BTK inhibitors, questions regarding their optimal sequencing are becoming increasingly relevant also for routine care. National and international treatment guidelines primarily recommend a switch to a different class of agents, e.g. Bcl-2 inhibitors, for patients with disease progression on a continuous covalent BTK inhibitor.[3] However, it is currently unclear which factors need to be considered for patients who develop intolerance to a BTK inhibitor, e.g. due to toxicity, and therefore have to discontinue treatment. It was previously demonstrated that a switch from ibrutinib or acalabrutinib to zanubrutinib in patients who had intolerance, mostly due to fatigue, hypertension, arthralgia, rash or atrial fibrillation, is feasible and can reduce or avoid recurrence of toxicity.[4] A general caveat regarding such analyses, which have also been conducted for acalabrutinib,[5] is the lack of a standardized definition of intolerance, which can lead to uncontrolled biases that can influence clinical decisions, such as re-imbursement considerations, availability of studies or frailty of patients. Patients with relapsed/refractory B-cell malignancies commonly present with a complex and heterogeneous mutational background, as the disease has been exposed to various selective pressures by treatments. The study by Xu *et al.* confirms this by demonstrating a high frequency of *TP53*, *SF3B1*, *ATM* and *NOTCH1* mutations in up to a third of patients who had discontinued ibrutinib or acalabrutinib. Interestingly, when looking at the prognostic relevance of these alterations, apart from *NOTCH1*, they were associated with a significantly shorter progression-free survival under zanubrutinib, suggesting similar molecular vulnerabilities as with other covalent BTK inhibitors (Figure 1).

Recent studies have shed light on the functional impact of *BTK* mutations in the context of BTK inhibitor resistance. The *BTK* C481S mutation is the most frequent *BTK* mutation arising in patients undergoing continuous BTK inhibition.[6] Functionally, this variant is associated with an altered binding site at the kinase domain of BTK, thereby leading to reduced affinity of covalent BTK inhibitors. Multiple other *BTK* mutations, such as T474I or T316A, have been described, which also confer treatment resistance and reduced binding affinity. In addition, other mutations, such as L528W, affect the activity of BTK and confer a kinase-dead state, despite an unaltered binding site. Several studies have reported L528W mutations occurring particularly after zanubrutinib treatment, possibly more commonly than after

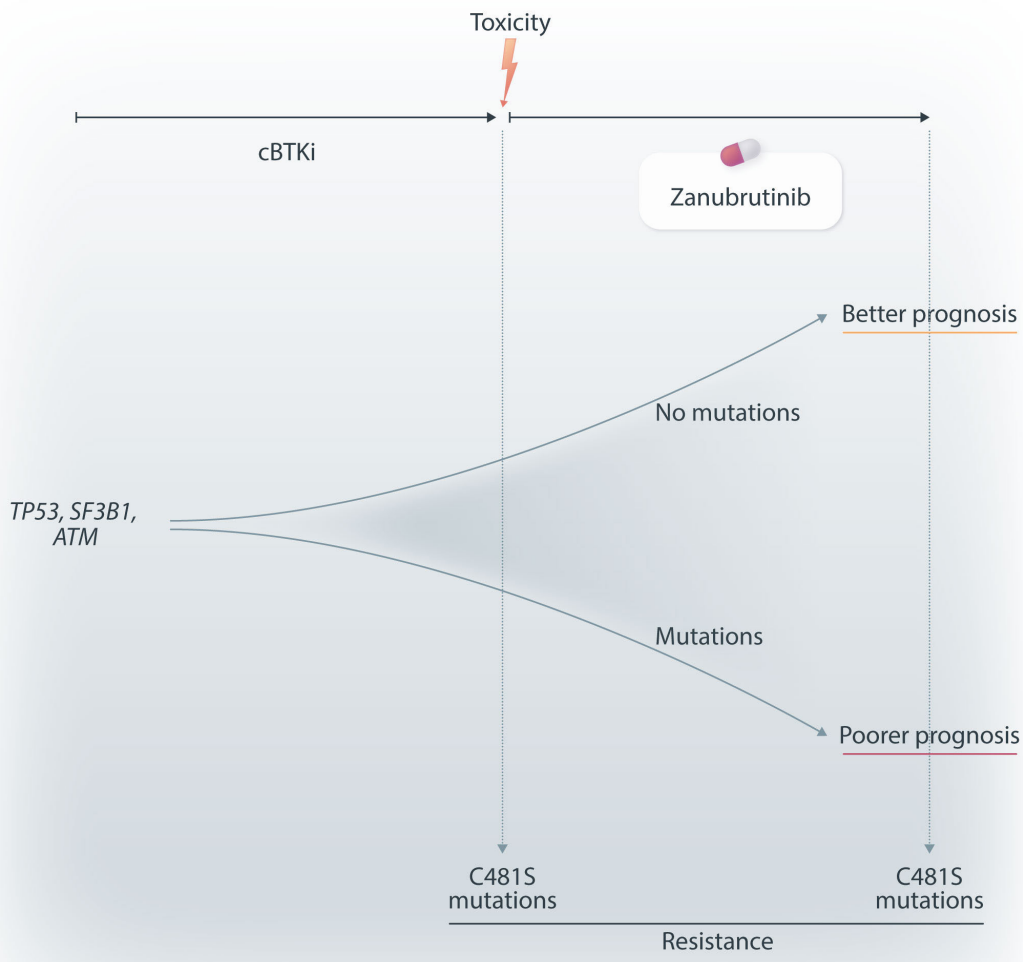

Figure 1. Landscape and impact of mutations with zanubrutinib treatment. cBTKi: covalent Bruton tyrosine kinase inhibitor.

the use of ibrutinib or acalabrutinib.[7] This observation is of high clinical relevance, as non-covalent BTK inhibitors, which have demonstrated efficacy also in the presence of C481S mutations, could be adversely affected in the context of L528W mutations.[8] Thus, the mutational pattern can have clinical implications regarding the sequence of giving zanubrutinib before or after pirtobrutinib. In the study by Xu *et al.* no L528W mutations were found in patients receiving zanubrutinib after prior ibrutinib or acalabrutinib therapy. With the caveat that the number of relapse samples sequenced was limited, this study at least does not suggest a particular over-enrichment of this variant in a cohort treated with ibrutinib/acalabrutinib followed by zanubrutinib.

Several open questions remain. As the number of patients progressing on zanubrutinib was limited in this cohort and the follow-up was relatively short, statistical analyses of prognostic factors were still heavily underpowered. Furthermore, our understanding of the clonal evolutionary patterns for patients discontinuing a BTK inhibitor due to toxicity and then undergoing treatment with a different BTK inhibitor is still incomplete. Most insights generated in this study are derived from the patients with chronic lymphocytic leukemia, from whom material for sequencing could be obtained from peripheral blood. However, the mutational patterns in nodal entities, such as mantle cell lymphoma and marginal zone lymphoma, are still understudied. Finally, given limited sample size and the heterogeneity of reasons for discontinuing treatment, further studies are required to better understand clinical and genomic features that might be associated with toxicity and intolerance to targeted agents.

Disclosures

No conflicts of interest to disclose.

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