

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Mechanisms of Resistance to BTK Inhibitors in Patients With Chronic Lymphocytic Leukemia



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H&O What are the mechanisms of action of ibrutinib and the next-generation Bruton's tyrosine kinase (BTK) inhibitors?

JW Ibrutinib and the second-generation covalent inhibitors acalabrutinib (Calquence, AstraZeneca), zanubrutinib (Brukinsa, BeiGene), and tirabrutinib hydrochloride (Velembro, Ono Pharmaceutical) inhibit BTK by binding to the cysteine residue at position 481 of *BTK*, and form a covalent bond with that amino acid. The BTK is then inactivated permanently. New BTK must be regenerated for the B-cell receptor pathway to turn back on.

Ibrutinib and the second-generation inhibitors differ primarily in their selectivity for BTK. Ibrutinib has several additional targets beyond BTK, while the newer-generation inhibitors are designed to be more selective for BTK. It is thought that this selectivity primarily impacts the agents' side effect profiles, rather than their efficacy.

H&O How is resistance defined, and how common is it?

JW Resistance is considered either intrinsic or acquired. Intrinsic resistance refers to patients who do not respond to therapy at all. Acquired resistance refers to patients who respond at first but then relapse during treatment. Intrinsic resistance to BTK inhibitors is rare among patients with chronic lymphocytic leukemia (CLL), but more common in other diseases. When a patient with CLL is

intrinsically resistant to a BTK inhibitor, the physician should consider alternative diagnoses such as Richter's transformation or even another hematologic malignancy. When a patient with CLL relapses within the first 2 years of treatment with a BTK inhibitor, the cause is often Richter's transformation. Relapses that occur after 2 to 3 years of treatment more commonly reflect progression of CLL.

It is difficult to estimate the number of patients who are resistant to ibrutinib. Resistance is much more common in the relapsed setting vs the frontline setting, and most of the data regarding resistance are drawn from the relapsed setting. In the frontline setting, most cases of resistance or relapse are in fact disease progression that occurs after treatment is stopped for toxicity or other reasons. We do not yet know the median progression-free survival of ibrutinib in the frontline setting, but recent data from the RESONATE-2 trial showed that 60% of patients were still progression-free after 6 years. In the relapsed setting, treatment with ibrutinib led to a median progression-free survival of approximately 44 months. However, these trials enrolled a more refractory population as compared with patients who are receiving BTK inhibitors in the clinic today.

H&O What are the mechanisms of resistance to ibrutinib?

JW The most common mechanism of resistance to ibrutinib appears to be a mutation of *BTK* at the binding site

of the drug. In most cases, the bond between the drug and BTK is changed from irreversible to reversible by a cysteine-to-serine mutation. Because the bond is temporary, the *BTK* eventually regains activity. All of the covalent BTK inhibitors have relatively short half-lives, so reversible inhibition of BTK is not very effective in this setting. Less commonly, there are mutations in phospholipase C gamma 2 (*PLCG2*), which is the kinase immediately downstream of *BTK* in the B-cell receptor pathway. Additional resistance mechanisms include clonal evolution and acquisition of other driver mutations in CLL.

For many patients who relapse, the mechanism is unknown. Researchers are currently evaluating other potential mechanisms.

The most common mechanism of resistance to ibrutinib appears to be a mutation of *BTK* at the binding site of the drug.

H&O Is the *BTK* mutation more common in the frontline or relapsed setting?

JW Among patients with CLL, those with relapsed disease are more likely to develop the *BTK* mutation and subsequent resistance than those in the frontline setting. At the 2020 American Society of Hematology (ASH) meeting, my colleagues and I presented results from a study that examined the acquisition of *BTK* mutations in patients who developed relapsed disease during treatment with ibrutinib or patients who had received ibrutinib for a long period and were responding well. The study found that mutations—and relapses—were much more common in patients with relapsed CLL. We lack understanding of resistance in the frontline setting, simply because so few of these patients develop progressive disease during treatment.

H&O What patient characteristics are associated with resistance?

JW The characteristics associated with resistance are better defined in the relapsed/refractory patient population. In our own institutional cohort of patients, we found that the complex karyotype is associated with resistance. The

17p deletion is important as well, especially when associated with the complex karyotype. Younger age appears to be a risk factor in some series. Other groups have shown that a high level of beta-2 microglobulin that does not decrease with therapy is associated with subsequent relapse. In general, many high-risk features known to decrease the efficacy of other drugs also decrease the efficacy of ibrutinib. The one possible exception is immunoglobulin heavy chain variable region (*IGHV*) mutation status, which does not appear to impact outcome with ibrutinib.

H&O What is known about resistance among the next-generation BTK inhibitors?

JW It is difficult to compare the prevalence of relapse with the second-generation covalent inhibitors vs ibrutinib because of differences in the patient populations enrolled in clinical trials. Most trials of the newer drugs enrolled patients who were less heavily pretreated than the patients in the original ibrutinib studies.

BTK mutations have been reported among patients treated with acalabrutinib. The issue has not been studied as much in zanubrutinib, although one would expect that *BTK* mutations would occur with any of the covalent inhibitors that share the same mechanism. More research is needed in this area.

H&O Are there strategies to decrease resistance?

JW Investigators are examining several strategies to decrease resistance. Combination therapy may be one strategy. Treatment with a single-agent BTK inhibitor is given for many years continuously. It is possible that the addition of venetoclax (Venclexta, Genentech/AbbVie) or another drug to ibrutinib might eliminate the disease clone entirely and allow therapy to stop. This type of combination treatment would be expected to decrease resistance owing to *BTK* mutations, which are seen only during active treatment. However, it is likely that other resistance mechanisms would arise in patients who are treated with multiple lines of combination therapy.

At Ohio State University, we are evaluating whether it is possible to add another therapy to ibrutinib at the time a mutation arises in order to avert resistance. For example, we are conducting a study in which venetoclax is given to patients who develop a mutation during treatment with ibrutinib. Another multicenter study is adding an antibody against the B cell–activating factor (BAFF) receptor among patients who develop a mutation but are not yet clinically resistant. These ongoing clinical trials will provide insight into the validity of this strategy.

H&O Are there any other areas of research in this setting?

JW A newer class of reversible BTK inhibitors is under investigation in preclinical and clinical studies. The goal is for these agents to inactivate *BTK* by binding to different sites than the cysteine residue. These drugs would potentially be active in the presence or absence of the cysteine-to-serine mutation. Trial data for LOXO-305 show a very high rate of activity in this patient population. LOXO-305 and other drugs are moving forward in their clinical development. It will be exciting to see how long these remissions last in patients who had previously been resistant to a covalent inhibitor. Future research will focus on the optimal sequencing of these drugs, and whether they should be administered in earlier lines of therapy.

Disclosure

Dr Woyach has performed consulting for AstraZeneca, AbbVie, ArQule, BeiGene, Janssen, Loxo, and Pharmacyclics.

Suggested Readings

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