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Ibrutinib: another string to its bow

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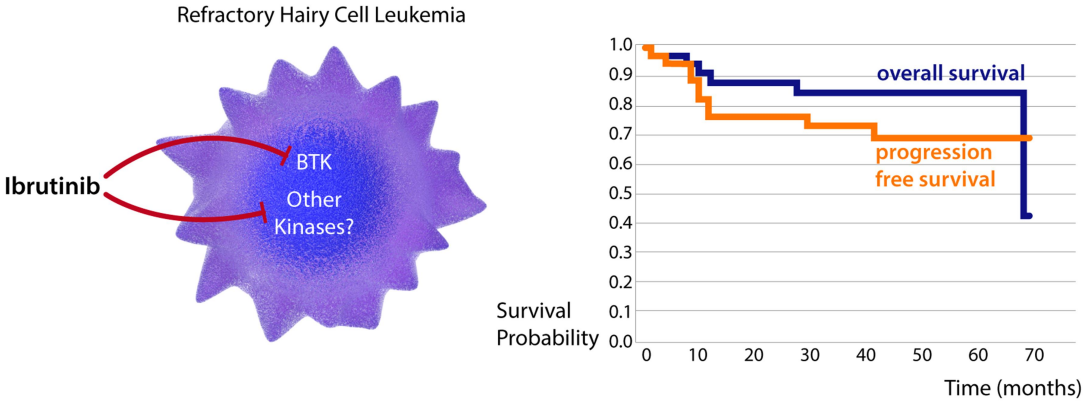

In this issue of Blood, Rogers and colleagues demonstrated the clinical benefit of ibrutinib for relapsed Hairy Cell Leukemia within a phase 2 clinical trial.[1]

In the last two decades, few drugs have made as rapid and as successful a journey from discovery to clinical implementation as ibrutinib. Ibrutinib is a highly potent irreversible, orally bioavailable, Bruton Tyrosine Kinase (BTK) inhibitor that targets the cysteine residue at position 481 (Cys-481) and blocks binding of adenosine triphosphate (ATP). This results in the inhibition of the phosphorylation of BTK and downstream targets, suppression of BCR signalling and cellular proliferation, as well as induction of apoptosis. Since its arrival on the scene in 2007,[2] ibrutinib has demonstrated profound antitumor activity in several B cell malignancies which transformed clinical outcomes of patients with chronic lymphocytic

leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldenström's macroglobulinemia (WM). [3-7]

In this important study, Rogers and colleagues show that the clinical utility of ibrutinib can be expanded further to Hairy Cell Leukemia (HCL).[1] HCL is a rare B cell malignancy characterized by two principal subtypes, a classic form which often features the presence of the V600E BRAF mutation and has generally good prognosis, and a variant form that exhibits limited response to standard treatment with purine analogues and poses a substantial therapeutic challenge.[8] Rogers and colleagues conducted a phase 2 multisite, open-label, single-agent study of ibrutinib for patients with HCL relapse and those for whom standard purine analogues were not a feasible therapeutic option. A total of 37 patients, 76% with classic and 24% with variant HCL, were enrolled in the study. Although the study did not meet the pre-specified overall response rate (ORR) of 50% at 32 weeks for the primary endpoint, remarkably, a majority of these heavily pre-treated HCL patients displayed durable response with a median overall survival (OS) of 69 months. Importantly, HCL subtype and other clinical features did not influence treatment response, and increasing age was the only factor that exerted a negative impact on clinical outcome. Ibrutinib was reasonably well tolerated and observed toxicities were comparable to those reported in other B cell malignancies.

Rogers and colleagues discovered that in similarity to CLL, deeper responses occurred with longer treatment duration: the overall response rate (ORR) in HCL rose from 24% at 32 weeks to 36% at week 48. But this is where the similarity between CLL and HCL response to ibrutinib ends. While ibrutinib in CLL impacts cell homing and migration, leading to a rapid release of tumor cells from proliferation niches associated with transient lymphocytosis, these effects were not observed in HCL. Furthermore, in CLL the collective effect of BTK inhibition on tumor cell homing, survival and proliferation determines response to ibrutinib. In HCL, however, durable benefit from ibrutinib treatment was observed even in patients with a persistent phosphorylation of BTK downstream target ERK. Finally, the principal mechanism of ibrutinib resistance in CLL involves BTK and PLCG2 mutations, consistent with continuous pressure on the drug target.[9] In contrast, HCL patients who developed resistance to ibrutinib displayed no such mutations. Taken together, the findings

by Rogers and colleagues imply that the clinical effect of ibrutinib in HCL patients, at least to some extent, may be independent of BTK inhibition.

The BTK independent activity of ibrutinib is becoming a fast-expanding area of research. Although remarkably selective for BTK, ibrutinib affects several other kinases that share the same cysteine residue in the ATP-binding site, including members of the TFK family (ITK, TEC, BMX, and RLK/TXK), the EGFR family (EGFR, ErbB2/HER2, ErbB4/HER4) as well as the kinases BLK and JAK3.[10] Consequently, elucidating the off-target effects of ibrutinib is shedding light on ibrutinib-associated toxicity.

We must not forget, however, that apart from treatment-associated toxicity, ibrutinib off-target activity may provide additional mechanisms that underpin its anti-tumor effect. The study by Rogers and colleagues is consolidating an appreciation that we should look beyond the BCR signaling-driven malignancies when considering ibrutinib as a therapeutic option. Future studies are required to fully understand how ibrutinib targets both malignant cells and its surrounding microenvironment irrespective of BTK inhibition. Understanding the influence of ibrutinib on different target proteins will inform strategies not only to counteract its toxicity but also to broaden its clinical application.

References:

1. Rogers K, Andritsos L, Wei L, et al. Phase 2 Study of Ibrutinib in Classic and Variant Hairy Cell Leukemia, Blood.

2. Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. Chem Med Chem. 2007;2:58–61.

3. Honigberg LA, Smith AM, Sirisawad M, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369(1):32-42.

4. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood. 2018;131(17):1910-1919.

5. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-516.

6. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017;129(16):2224-2232.

7. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015;372(15):1430-1440.

8. Cross M, Dearden C. Hairy Cell Leukaemia. Curr Oncol Rep. 2020 Apr 16;22(5):42.

9. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med. 2014;370(24):2286-2294.

10. A. Berglöf A, Hamasy S, Meinke, et al. Targets for Ibrutinib beyond B cell malignancies. Scand J Immunol. 2015; 82: 208–217.

Figure legend

Ibrutinib provides a new therapeutic solution for refractory HCL patients. Treatment with ibrutinib resulted in durable responses in these patients irrespective of the status of BCR signaling.