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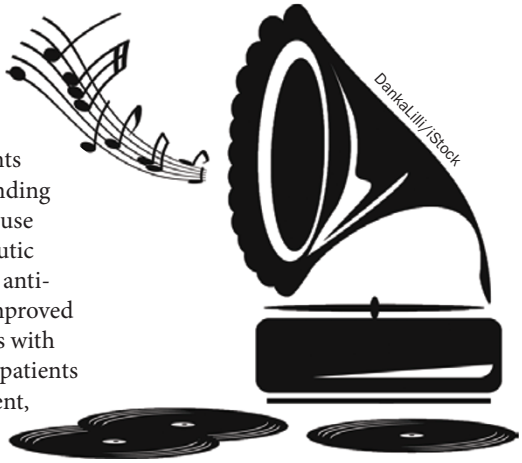
TARGETED THERAPIES

Ibrutinib resonates with us



Treatment of chronic lymphocytic leukaemia (CLL) has consisted mainly of a combination of chemotherapeutic agents that have failed at extending survival. Although the use of the immunotherapeutic agent ofatumumab (an anti-CD20 antibody) has improved the outcome of patients with refractory CLL, not all patients respond to this treatment, and the options for treating relapsed disease are limited and very toxic. Recently, the finding that B-cell-receptor signalling—and its downstream effector, Bruton's tyrosine kinase (BTK)—is a driving factor of CLL, has led to consider the inhibition of this pathway as a hopeful choice to treat this disease.

Ibrutinib is an oral inhibitor of BTK that suppresses CLL-cell proliferation. On the basis of promising results of phase II trials that prompted the FDA to grant accelerated approval of ibrutinib for patients with CLL, Byrd and colleagues initiated a multicentre, randomized, phase III study (RESONATE), to compare the effectiveness of ibrutinib administered once daily versus weekly ofatumumab, in patients with relapsed or refractory CLL.

The primary end point was progression-free survival (PFS), and secondary end points were overall survival and response rate. At a median follow-up of 9.4 months, ibrutinib significantly improved PFS (not reached in the ibrutinib group—with a PFS rate of 88% at 6 months—compared with 8.1 months in the ofatumumab group). At 12 months, the overall survival rate was 90% in the ibrutinib group and 81% in the ofatumumab group, and the overall response rate was significantly greater in the ibrutinib group (42.6%) compared with the ofatumumab group (4.1%). The toxicity reports showed that ibrutinib can be safely administered even in heavily pretreated and elderly patients. However, despite its efficacy, a proportion of patients, albeit small, relapse during treatment with ibrutinib.

In another study from the same authors, a possible mechanism of resistance to ibrutinib is described. They carried out whole-exome sequencing at baseline and at the time of relapse on samples from six patients with acquired resistance and identified mutations through functional analysis. They found that resistance to ibrutinib involves mutation of a cysteine residue in BTK where the inhibitor binds. Two additional mutations were also identified in PLCγ2, downstream of BTK, both potentially gain-of-function mutations that lead to autonomous B-cell–receptor activity.

These studies illustrates how the understanding of the biology of CLL can drive and shape the future of its treatment.

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Original articles Woyach, J. A. *et al.* Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N. Engl. J. Med.* doi:10.1056/NEJMoa1400029 | Byrd, J. C. *et al.* Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N. Engl. J. Med.* doi:10.1056/NEJMoa1400376