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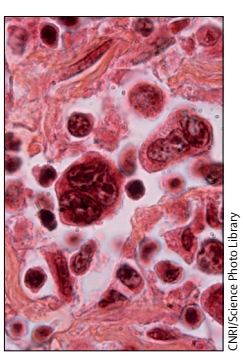
# Venetoclax: a chance for patients with chronic lymphocytic leukaemia previously treated with ibrutinib

In recent years, biological and clinical research has identified several targeted agents that are changing the management of patients with chronic lymphocytic leukaemia. In clinical trials,[1] the B-cell receptor inhibitor ibrutinib has led to durable responses and longer survival (overall and progression-free) than chemotherapy in patients with this disease. Ibrutinib is now largely used in clinical practice in patients with chromosome 17p deletions or *TP53* mutations and relapsed or refractory chronic lymphocytic leukaemia. More recently, the drug has also been approved in the USA and European Union as a front-line therapy for chronic lymphocytic leukaemia.[1] However, many patients discontinue ibrutinib because of adverse events such as atrial fibrillation, infections, and cytopenias. Another common reason for treatment discontinuation is disease progression, which is observed most frequently in patients with *TP53* mutations or complex karyotypes.[2,3] Mutations conferring resistance to ibrutinib are also commonly found in patients with high-risk genetic landscapes or who have disease progression during ibrutinib treatment.[4,5] Outcomes after ibrutinib discontinuation are poor,[2,3] and few treatment options are available for such patients. Therefore, treatment options for patients with relapsed or refractory disease previously treated with ibrutinib are a primary unmet medical need in the management of chronic lymphocytic leukaemia, especially given the increasing use of this drug in clinical practice.

Venetoclax is a first-in-class, oral, selective inhibitor of BCL-2 (apoptosis regulator Bcl-2), which regulates cell apoptosis. Inhibition of BCL-2 in chronic lymphocytic leukaemia cells leads to a high pro-apoptotic effect that is independent of *TP53*. Deep responses with no evidence of minimal residual disease have been described in patients with relapsed or refractory disease given venetoclax monotherapy, including those with *TP53* mutations.[6,7] Combined with rituximab, venetoclax led to a high proportion of patients being negative for minimal residual disease in a phase 1b study.[8] Given the activity of venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia, including in those who have progressed on ibrutinib,[9] Jeffrey Jones and colleagues[10] did a multicentre, open-label, phase 2 trial to assess the activity and safety of venetoclax in patients with chronic lymphocytic leukaemia previously treated with ibrutinib; the results of an interim analysis are reported in *The Lancet Oncology*. Of the 91 patients included in the activity and safety analyses, 50 (55%) had discontinued ibrutinib because of disease progression, 30 (33%) because of adverse events, and 11 (12%)



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because maximal clinical benefit was achieved (n=6), the defined course of treatment was completed (n=3) or unspecified reasons (n=2).[10]

The study included patients with clinical and biological characteristics indicative of a poor prognosis and who had been heavily pre-treated, with ibrutinib being the last therapy they received before enrolment. 50 (75%) of 67 patients were negative for mutations in immunoglobulin heavy-chain variable region genes, 42 (47%) of 90 patients had a deletion in chromosome 17 [del(17)(p13·1)], and 29 (33%) of 87 patients had a *TP53* mutation. Additionally, *BTK* or *PLCG2* mutations were found in 17 (81%) of 21 tested patients.

59 (65%, 95% CI 53–74) of the 91 patients in the study had an overall response as per investigator's assessment. Deep responses with no evidence of cytometric minimal residual disease were detected in the peripheral blood of 24 (42%) of 57 patients who showed a response and underwent this assessment for minimal residual disease. Responses were observed independently of the reason for stopping ibrutinib and were not affected by the presence of a *TP53* mutation. Notably, responses were also recorded in patients who progressed on ibrutinib because of the emergence of mutations; 12 (71%) of 17 patients with known ibrutinib-resistance mutations had an overall response. Furthermore, a decrease in the allelic frequency of Cys481Ser *BTK* mutations during up to 72 weeks of venetoclax treatment was observed in eight patients with serial data available.

12-month progression-free survival was 75% (95% CI 64–83) and 12-month overall survival was 91% (83–95). These outcomes are similar to those previously reported for venetoclax in patients with relapsed or refractory disease who had previously only been treated with chemoimmunotherapy.[4] Additionally, the safety profile of venetoclax was consistent with previous reports of single-drug venetoclax in the same population.[4–6]

The results of this trial show the capacity of venetoclax, through BCL-2 inhibition, to overcome not only the negative effect of a *TP53* mutation, but also ibrutinib resistance due to the emergence of mutations. This new information is important for optimal management of patients with chronic lymphocytic leukaemia progressing on ibrutinib. Taken together, the results of this trial are reassuring and have relevant clinical implications, especially now that ibrutinib has been approved as a first-line treatment for patients with chronic lymphocytic leukaemia. As ongoing randomised trials investigate front-line combination regimens involving venetoclax, the next question to be addressed will be how to treat patients who progress after initial therapy with this drug.

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# Bipolar androgen therapy: an intriguing paradox

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In *The Lancet Oncology*, Benjamin A Teply and colleagues[1] report a phase 2 trial in men with metastatic castration-resistant prostate cancer with progression on an androgen receptor pathway inhibitor, enzalutamide, who were treated with bipolar androgen therapy (BAT). It is a novel and intriguing concept.

Castration-resistant prostate cancer occurs through numerous mechanisms, including androgen receptor