Ibrutinib monotherapy in chronic lymphoid leukaemia

Ibrutinib, compared with ofatumumab, can substantially improve progression-free survival (PFS), overall survival, and response in patients with previously treated chronic lymphoid leukaemia, according to new research published in the *New England Journal of Medicine* and presented at ASCO. John Byrd and colleagues presented results from a phase 3 trial comparing the efficacy of ibrutinib (a Bruton-tyrosine-kinase inhibitor) with ofatumumab in patients with relapsed or refractory chronic lymphoid leukaemia or small lymphocytic lymphoma. They randomly assigned 391 patients to receive oral ibrutinib (n=195) or intravenous ofatumumab (n=196). Median follow-up was 9·4 months (range 0·1–16·6). The researchers found that ibrutinib substantially improved PFS in the participants, compared with ofatumumab. Median duration of PFS was not reached in the ibrutinib group (88% of patients were progression free at 6 months) compared with a median of 8·1 months in the ofatumumab group. The hazard ratio for progression or death in the ibrutinib group was 0·22 (95% CI 0·15–0·32; p<0·001). Ibrutinib also substantially improved overall survival (hazard ratio for death 0·43; 95% CI 0·24–0·79; p=0·005), the researchers noted. 83 (43%) of patients treated with ibrutinib had a partial response compared with eight (4%) of those with ofatumumab. The most frequent non-haematological adverse events that occurred in at least 20% of patients included diarrhoea, fatigue, pyrexia, and nausea in the ibrutinib group, and fatigue, infusion-related reactions, and cough in the ofatumumab group.

Thorsten Zenz (National Center for Tumour Diseases, Heidelberg, Germany) says: "The study demonstrates the power of inhibitors of the B cell receptor in chronic lymphoid leukaemia." The current study as well as previous work by Byrd and colleagues can change the practice in chronic lymphoid leukaemia, Zenz comments.

According to Jason Westin (MD Anderson Cancer Center, TX, USA), the implications of the study's findings will set a new high standard for future trials. He comments: "With these results, it may be challenging for future single agent comparison trials of targeted inhibitors to have sufficient power to show further meaningful improvements without accrual of very large numbers of patients or long follow-up time."

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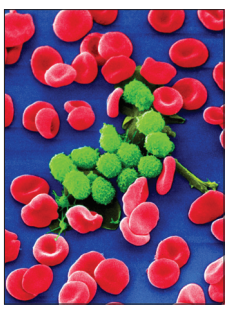

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For **Byrd and colleagues' paper** see *N Engl J Med* 2014; published May 31. DOI:10.1056/NEJMoa1400376

Enzalutamide in castration-resistant prostate cancer

Enzalutamide, an oral androgen-receptor inhibitor, prolongs the time until radiographic progression and improves overall survival in men with metastatic castration-resistant prostate cancer who have not previously undergone chemotherapy, according to the results of a multi-national, randomised phase 3 study published in the *New England Journal of Medicine*. The study was presented at ASCO by Andrew Armstrong. One group of patients received a daily dose of enzalutamide (160 mg) and the other group received placebo. Treatment with enzalutamide resulted in better overall survival than with placebo (hazard ratio 0·71, 95% CI 0·60–0·84; p<0·001), and longer radiographic progression-free survival (0·19, 0·15–0·23; p<0·001). The median time until initiation of chemotherapy was 28·0 months in the enzalutamide group versus 10·8 months in the placebo group (0·35, 0·30–0·40; p<0·001). The data and safety committee was moved to recommend that the study be unmasked and enzalutamide offered to those in the placebo group.

"The message from the study is very clear: this drug has significant levels of activity against prostate cancer", coauthor Tomasz Beer (Oregon Health and Science University Knight Cancer Institute, USA) told *The Lancet Oncology*. Enzalutamide has already shown efficacy in patients who have previously undergone chemotherapy; if its licence is extended to include the pre-chemotherapy setting, it is likely to change clinical practice. "Patients will have the choice of having enzalutamide before chemotherapy", notes Chris Parker (Royal Marsden Hospital and Institute of Cancer Research, Sutton, UK). "It is a much more attractive proposition because it is effective and much better tolerated than chemotherapy, and patients tend to want to delay chemotherapy as much as reasonably possible." Beer advocates exploring the possibility of introducing the agent even earlier in the course of the disease. "Prostate cancer is really addicted to androgen-receptor signalling; with conventional androgen deprivation we haven't targeted the system nearly as completely as we originally thought", he explained. Primary hormonal therapy might be more effective with the more comprehensive blockade of the androgen receptors offered by the incorporation of enzalutamide.

Questions still remain over how best to sequence the various drugs in this field, the potential for combination therapies, and whether there are molecular markers that can predict and explain response and resistance.

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