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HAEMATOLOGICAL CANCER

Idelalisib for CLL — risky benefit

Several drug combinations are available for the frontline treatment of patients with chronic lymphocytic leukaemia (CLL), but the risk of disease relapse remains high. On the basis that the PI3Kδ isoform is mainly expressed in leukocytes, Andrew Zelenetz and colleagues conducted a phase III trial to evaluate the addition of the PI3Kδ inhibitor idelalisib to bendamustine and rituximab, the standard-of-care regimen for patients with relapsed CLL.

All patients enrolled in this study were randomly assigned to receive bendamustine and rituximab supplemented with either idelalisib ($n = 207$) or placebo ($n = 209$). The interim analysis results, at a median follow-up of 11 months, revealed that 190 of 260 progression-free survival (PFS) events (75%) had occurred; owing to the high observed efficacy of idelalisib, the study was halted and unblinded. At a median follow-up of 14 months, the median PFS duration was longer for patients receiving idelalisib than for those receiving placebo (20.8 months versus 11.1 months; $P < 0.0001$). The benefit in PFS was consistent across most risk-defined patient subgroups. This study was not adequately powered to show an overall survival benefit but, at the time of reporting, median overall survival was not reached for patients in the idelalisib group versus 31.6 months for the placebo group.

Treatment with idelalisib was associated with an increased risk of toxicities. The percentage of patients with adverse events leading to treatment discontinuation was higher in the idelalisib group than in the placebo group (28% versus 14%). The most common adverse events leading to treatment discontinuation were pneumonia (4% versus 2%), diarrhoea (2% versus none) and pyrexia (2% versus <1%). The most common all-grade adverse events in patients receiving idelalisib were neutropenia (60%) and febrile neutropenia (23%), and in the placebo group were neutropenia (47%) and thrombocytopenia (13%). Importantly, the frequency of infections was higher for patients in the idelalisib group (69% versus 59%), and more patients died from infections in the idelalisib group than in the placebo group (six versus three).

Data from subsequent analysis are awaited to determine whether the impressive PFS advantage observed with idelalisib translates into an overall survival benefit. In the absence of such data, however, great caution must be taken when prescribing this treatment, which is associated with a substantial increase in toxicities.

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ORIGINAL ARTICLE Zelenetz, A. D. *et al.* Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(16)30671-4 (2016)