HAEMATOLOGICAL CANCER

Alliance to iLLUMINATE the chemo-free sign

> survival and toxicity results … support the use of monotherapy

Treatment regimens for patients with chronic lymphocytic leukaemia (CLL) increasingly include targeted agents (such as the inhibitor of BTK ibrutinib or the anti-CD20 antibodies rituximab and obinutuzumab) rather than cytotoxic agents (for example, the DNA alkylating agents chlorambucil and bendamustine). New evidence supporting benefit with targeted therapies was presented at the 2018 Annual Meeting of the American Society of Hematology (ASH).

In the phase III iLLUMINATE trial, older patients (≥65 years of age) with untreated CLL were randomly assigned to receive ibrutinib plus obinutuzumab (experimental arm; $n = 113$) or chlorambucil plus obinutuzumab (control arm; $n = 116$). Progression-free survival (PFS) was longer in the experimental arm than in the control arm: not reached versus 19.0 months (HR 0.23; $P < 0.0001$). "Importantly, the PFS benefit was maintained in all subgroups of patients regardless of high-risk genomic features. The high-risk subgroup in this trial included 65% of patients, for whom the reduction risk was 85% compared with conventional therapy," explains lead investigator Carol Moreno. At 31.3 months, median overall survival (OS) had not been reached in either group. Grade 3–4 adverse events (AEs) were reported in 68% and 70% of patients in the experimental and control arms, respectively.

In the Alliance A041202 study, also presented at ASH 2018, older patients with untreated CLL were randomly assigned to receive bendamustine plus rituximab ($n = 183$), ibrutinib ($n = 182$) or ibrutinib plus rituximab ($n = 182$). 2-year PFS was 74% with bendamustine plus rituximab, 87% with ibrutinib (HR 0.39; $P < 0.001$ relative to bendamustine plus rituximab) and 88% with ibrutinib plus rituximab (HR 0.38; $P < 0.001$). "We did not observe differences in OS for reasons that include the presence of other risks in this patient population, a short follow-up duration and a trial design that allowed crossover," says Jennifer Woyach. Grade 3–5 haematological AEs were reported in 61% of patients receiving bendamustine plus rituximab, 41% receiving ibrutinib and 39% receiving ibrutinib plus rituximab; non-haematological grade 3–5 AEs were reported in 63%, 74% and 74% of patients, respectively.

Results of another study of ibrutinib in patients with CLL that had been presented at the previous ASH Annual Meeting, in 2017, have now also been published. This phase II trial involved a cohort with a median age of 65 years, 87% of whom had received prior treatment. Patients were randomly assigned to receive ibrutinib either as monotherapy or in combination with rituximab ($n = 104$ in each group). 2-year PFS was 95% with monotherapy and 92.5% with combination therapy; the estimated 3-year OS was 92% versus 89%. Grade 3–4 treatment-emergent AEs were reported in 64% of patients receiving monotherapy and 65% receiving combination therapy.

Among patients receiving monotherapy, 20.2%, 61.5% and 10.6% had a complete remission (CR), partial remission and partial remission with lymphocytosis, respectively. In the combination group, these percentages were 26.5%, 62.5% and 3.8%, respectively. The time to any type of response was similar in both groups (median 4.7 months and 4.8 months with monotherapy and combination therapy), but the median time to achieve a CR was shorter with combination therapy (11.5 months versus 22.2 months). Combination therapy was associated with lower levels of minimal residual disease (MRD) in bone marrow than monotherapy at 12 months (18.5% versus 34.4%) and 24 months (12.2% versus 19.8%).

The survival and toxicity results of both trials comparing ibrutinib alone or combined with rituximab support the use of monotherapy. However, response rates and MRD status results of the phase II trial warrant consideration of the combination regimen. Results of studies aiming to identify the patients who will derive most benefit from this option are awaited.

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ORIGINAL ARTICLES Moreno, C. et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(18)30788-5 (2018) | Woyach, J. A. et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1812836 (2018) | Burger, J. A. et al. Randomized trial of ibrutinib versus ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood* https://doi.org/10.1182/blood-2018-10-879429 (2018)