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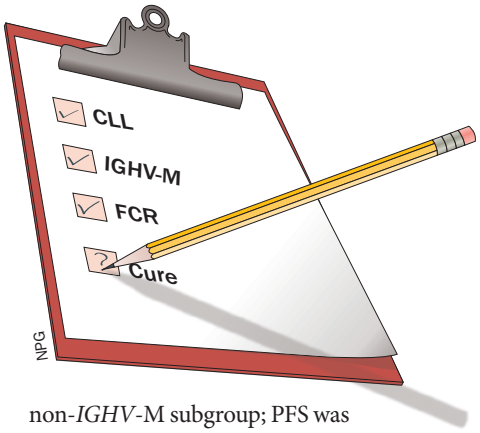
HAEMATOLOGICAL CANCER

Can FCR be curative in CLL?



Upfront chemotherapy remains the standard of care for chronic lymphocytic leukaemia (CLL). New data confirm that fludarabine and cyclophosphamide (FC) chemotherapy is inferior to chemoimmunotherapy with FC plus rituximab (FCR), and indicate that FCR can result in long-term disease control, and possibly cures.

In the German CLL Study Group (GCLLSG) CLL8 trial, 817 treatment-naive patients with CLL received six cycles of FC or FCR. At a median follow up of 5.9 years, survival outcomes were significantly better in the patients treated with FCR: median progression-free survival (PFS) 56.8 months versus 32.9 months ($P<0.001$); median overall survival not reached versus 86.0 months ($P=0.001$). These benefits came at the expense of an increased frequency of prolonged neutropenia within 12 months of treatment (16.8% versus 8.8%); however, the rate of secondary malignancies, including Richter transformation, was decreased (13.1% versus 17.4%).

The benefit of FCR treatment over FC therapy was observed across most genetic subgroups of patients. Of note, patients with *IGHV*-mutated (*IGHV*-M) disease had prolonged PFS after FCR therapy compared with those without *IGHV* mutations (5-year PFS 66.6% versus 33.1%), and responded better to this regimen than to FC (5-year PFS 66.6% versus 36.2%). Interestingly, at least 90% of evaluable patients with *IGHV*-M CLL and trisomy 12, 13q(del), or 11q(del) who received FCR were alive beyond 7 years.

Data from a second long-term study, in the 300 patients treated in the original phase II trial of FCR, support the particular benefit of FCR for patients with *IGHV*-M CLL and, moreover, suggest that this treatment can be curative. At a median follow up of 12.8 years, PFS was 53.9% in the *IGHV*-M subgroup versus 8.7% in the non-*IGHV*-M subgroup; PFS was 79.8% among the *IGHV*-M patients who achieved minimum residual disease negativity (50.7%), and this status was maintained in all of 15 patients who were reassessed. Importantly, no relapses were seen beyond 10.4 years in the *IGHV*-M subgroup, indicating that >50% of these patients might be cured.

"These results are of particular importance in light of the advent of novel targeted agents, such as ibrutinib, idelalisib and venetoclax, because they demonstrate that chemoimmunotherapy with FCR may yield very good long-term outcomes in molecularly-defined subgroups of patients with CLL," explains Michael Hallek, Chair of the GCLLSG. "Therefore, novel substances should be tested against this standard before concluding on their definitive value," he adds.

These findings support a new paradigm of CLL therapy guided by *IGHV* status. FCR might be difficult to supersede as standard therapy for patients with *IGHV*-M disease (particularly those with specific cytogenetic aberrations), in whom cures might be possible; however, alternative treatments will probably be pursued for other patients.

David Killock

Original article Fischer, K. *et al*. Long term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood* doi:10.1182/blood-2015-06-651125 | Thompson, P. A. *et al*. Fludarabine, cyclophosphamide and rituximab achieves long-term disease-free survival in *IGHV*-mutated chronic lymphocytic leukemia. *Blood* doi:10.1182/blood-2015-09-667675