Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the national cancer research institute CLL206 trial.

Pettitt AR, Jackson R, Carruthers S, Dodd J, Dodd S, Oates M, Johnson GG, Schuh A, Matutes E, Dearden CE, Catovsky D, Radford JA, Bloor A, Follows GA, Devereux S, Kruger A, Blundell J, Agrawal S, Allsup D, Proctor S, Heartin E, Oscier D, Hamblin TJ, Rawstron A, Hillmen P.
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Despite advances in treatment for CLL, finding an effective therapy for patients with defects in the p53 pathway remains a clinical challenge. Approximately 10-15% of patients have p53 dysfunction, which most often results from deletion on chromosome 17 (del(17p)) and is frequently accompanied by mutation in the *TP53* gene on the remaining p53 allele, rendering the protein totally inactive. As well as this bi-allelic loss of the *TP53* gene, a minority of patients have mono-allelic loss of *TP53*. However, for both scenarios, the outcome for patients is poor: patients are resistant to chemotherapy and have a shorter survival. In the recent CLL8 trial, which demonstrated the effectiveness of FCR chemoimmunotherapy for the majority of CLL patients, del(17p) remained a predictor of poor response.

p53 is a transcription factor that directs the cellular response to DNA damage, and it is activated following treatment with chemotherapeutic drugs and ionising radiation that induce DNA strand breaks. A functional p53 pathway facilitates cell cycle arrest (and repair of DNA damage) or apoptosis (and therefore eradication of cells with excessive DNA damage). Conversely, cells with p53 dysfunction are unable to activate an effective DNA damage response, which therefore renders the cells resistant to chemotherapy.

This aim of this study was to evaluate a therapy for patients with *TP53* defects that did not include DNA damaging agents and therefore circumvented the need for an intact p53 signalling pathway for response. The authors hypothesised that patients with *TP53* defects would respond to a combination of Alemtuzumab, (an anti-CD52 monocloncal antibody that had previously shown efficacy in patients with *TP53* defects) and methylprednisolone, a glucocorticoid which is known to reduce lymphadenopathy. The rationale of the combination was that methylprednisolone would redistribute CLL cells into the bloodstream, where they would be susceptible to alemtuzumab.

39 patients with del(17p) (loss in >20% of cells by FISH) were selected for this study. Importantly, this cohort contained previously untreated (17) as well as treated (22) patients. Patients received 30mg alemtuzumab (3 times per week) for 16 weeks in combination with $1g/m^2$ methylprednisolone for 5 consecutive days, which was repeated every 4 weeks for 4 cycles, and all patients received at least one dose. The median age was 62, and 46% of the patients were Binet stage C. Grade 3/4 infection occurred in 50% of patients and grade 3/4 haematologic toxicity occurred in 67% of patients. Although the infection rate was high, this was lower (29%) in younger patients (<60) and is comparable with the infection rate seen in younger patients in the CLL8 trial (23% in patients <65). The overall response rate was 85% and the complete response was 36%, but those patients that were previously untreated had an impressive 65% complete response rate. The progression-free survival was 18.3 months for previously untreated patients, which is superior to any other induction therapy for this group of patients.

In summary, CLL patients with *TP53* defects have progressive disease that is difficult to treat effectively, and which is resistant to DNA damaging therapy that contains e.g. Fludarabine and cyclophosphamide. The combination of alemtuzumab and methylprednisolone gives an impressive response rate and also improved overall survival, particularly for previously untreated patients. The

toxicity is significant, although in younger patients is similar to that resulting from current frontline therapy with FCR. These data, together with the promising results of early trials with agents that target B-cell receptor signalling, herald the beginning of stratified therapy for CLL patients, based on molecular profiling.

Reviewed by Elaine Willmore