Fludarabine, Cyclophosphamide and Rituximab in salvage therapy of Waldenstrom Macroglobulinemia

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Fludarabine and Cyclophosphamide are synergistic with Rituximab *in vitro* in lymphoma cell lines, and the administration of the three drugs is associated with higher response rates in chronic lymphocytic leukemia and other lymphoprolipherative disorders. FCR proved to be active in Waldenstrom Macroglobulinemia (WM) leading to rapid disease control and to good quality of responses (30% of CR plus VGPR) in a series of 43 previously treated or first line treatment patients. Prolonged myelosuppression induced by this regimen and the concerns about purine analogs treatment in WM lead the conclusion that this regimen should be avoided in younger patients in first line treatment.

To define the efficacy and tolerability and late toxicity of FCR as salvage regimen we retrospectively analyzed 40 patients. At the time of FCR treatment median age was 67 years (27-78), sex ratio M/F 28/12, 14 patients (35%) presented with refractory disease. Median number of prior regimens was 1 (range 1-4) being median time from WM diagnosis and from last treatment to FCR administration of 63 and 19.6 months respectively. The 22% of patients had been previously treated with immunochemotherapy including rituximab. Splenomegaly and or lymphadenopathy were present in 35% of cases. Median IgM level was 4780 mg/dL (881- 10900). FCR regimen was administered every 4 weeks and consisted of: Rituximab 375 mg/sqm iv day 1, Fludarabine 25 mg/sqm iv day 1-3, Cyclophosphamide 250 mg/sqm iv day 1-3.

The overall response rate (ORR) was 80%, including 10% complete remissions (CRs) and 22.5% very good partial remissions (VGPRs) and 47.5% PRs. The 17.5% of patients remained in stable disease while disease progression rate was of 2.5% A progressive significant decrease of IgM levels was observed in responders from the end of therapy and during follow-up.

None of the clinical and biological variables considered had a significative impact in the achievement of ORR or good quality of response (CR plus VGPR).

Median PFS has not been reached after a median follow-up of 49 months, median EFS was reached after 77 months.

Overall 176 courses of FCR treatment were administered, median number 6 (range 2-6). In the 37.5% of patients fewer than 6 cycles were administered being cytopenia the major cause of discontinuation (53%). ORR obtained in this group of patients was of 80%. None of clinical and disease variables analyzed had a prognostic significance for treatment discontinuation. Grade 3-4 neutropenia occurred in 61% of courses. Ten episodes of FUO and 2 major infections were recorded during treatment. Six major infections were recorded during follow-up, three of them occurring in patients with delayed neutropenia. Infections was cause of death in 2 cases.

FCR regimen is active and well tolerated in previously pre-treated patients with symptomatic WM giving similar results to those observed when used in first line treatment. The high incidence of neutropenia did not translate in major infectious episodes. The evidence of good quality of responses obtained in patients discontinuing treatment before the sixth cycle and the tardive prolonged myelosuppression warrant to optimize the dosages and the duration of the combination treatment.