MULTICENTER STUDY OF FLUDARABINE, CYCLOPHOSPHAMIDE AND RITUXIMAB IN UNTREATED AND PREVIOUSLY TREATED WALDENSTROM MACROGLOBULINEMIA

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Rituximab (R) is an active and well tolerated agent in the treatment of untreated or refractory/relapsed Waldenstrom's Macroglobulinemia (WM) patients. Furthermore, there is evidence that the association of R with chemotherapy may improve the quality and the duration of responses. Fludarabine and Cyclophosphamide (FC) are synergistic with R *in vitro* in lymphoma cell lines, and the administration of the three drugs is associated with higher response rates in other lymphoprolipherative disorders. We designed a phase II study to assess tolerability and safety of FCR in symptomatic WM pts previously untreated or relapsed/refractory after one line of chemotherapy. Therapy consisted of: rituximab 375 mg/sqm on day 1, fludarabine 25 mg/sqm iv and ciclophosphamide 250 mg/sqm iv on days 2 to 4. Courses were repeated every 28 days for a maximum of 6 cycles. Forty-three patients were enrolled with a median age of 65 years; 65% of patients received FCR as first line treatment. Thirty-nine (87%) patients completed 4 courses of therapy and were evaluated for response, the remaining 4 unevaluable cases were considered as failures. In fifteen patients (35%) fewer than 6 cycles were administered; the primary reason for therapy discontinuation was persisting cytopenia requiring continuative supportive treatment with growth factors (9 patients). On an intent-to treat basis the overall response rate was 79% including 12% CRs, 21% nCRs, 42% PRs and 4% MRs. The major response rate being 74%. $ß_2$ microglobulin level was the only variable significantly predictive for the achievement of a major response. During follow-up an amelioration of response was observed in 5 cases, 1 patient in minor response converted in PR and 4 patients in nCR achieved a CR. A progressive significant decrease of IgM levels was observed in responders from the end of therapy and during follow-up until the eighteenth

month (*P<.001*). With a median follow-up of 24.8 months the TTP rate of responding patients was 87.6%. Major toxicity was grade 3-4 neutropenia occurring in the 45% of courses. Long lasting episodes of neutropenia, persisting after the last course of treatment were recorded in 19 patients. Eight major infections were documented being cause of death in 3 patients. Two patients, previously heavily pretreated with alkylating agents, developed a myelodysplastic syndrome after 5 and 24 months respectively

Our results demonstrated that FCR produces rapid responses with high rates of CR and nCR; myelosuppression was the most common cause of early discontinuation leading to a high incidence of prolonged episodes of neutropenia, further studies are needed to optimize the dosages and the duration of the combination treatment. FCR could be considered an effective salvage regimen able to neutralize adverse prognostic factors. In younger patients in first line treatment FCR should be avoided on the basis of the potential impact on the development of secondary malignancies and on the myelosuppressive effect of this regimen that may impair stem cell collection.