Efficacy and safety of purine analogs in patients with Waldenström's macroglobulinemia

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Both cladribine and fludarabine, used alone or in combination, have been extensively evaluated in untreated as well as previously treated WM patients. When used as a single agent ,the overall response rate have ranged from 40– to 90% of patients who received primary therapy, whilst in the salvage setting responses have ranged from 30% to 50%. Combination therapy with rituximab has been investigated as both first line and salvage therapy in WM. Laszlo et al evaluated the combination of subcutaneous cladribine with rituximab in 29 WM patients with either untreated or previously treated disease. With a median follow-up of 43 months, the overall response rate observed was 89.6%, with seven complete responses (CR), 16 partial responses, and three minor responses. In a study by the WMCTG, the combination of rituximab and fludarabine was administered to 43 WM patients, 32 (75%) of whom were previously untreated. The overall response rate was 95.3%, and 83% of patients achieved a major response. The median time to progression was 51.2 months in this series. The combination of fludarabine plus cyclosphosphamide (FC) was also evaluated by Tamburini et al involving 49 patients, 35 of whom were previously treated. Seventy-eight percent of the patients in this study achieved a response and median time to treatment failure was 27 months. Tedeschi et al recently completed a multicenter study on with fludarabine, cyclophosphamide and rituximab (FCR) in 43 symptomatic WM patients with untreated or relapsed/refractory disease to one line of chemotherapy. The overall response rate was 89%, with 83% of patients attaining a major remission, and 14% a complete response. With a median follow up of 15 months, the median progression free survival for this study has not been reached. Updated data were presented in Newport in 67 patients with a TTP of 51 months. The french experience of FCR in 82 patients will be presented (25 untreated and 57 in relapse). The ORR rate was 84.5% with 6MR, 32PR, 26VGPR and 5 CR. With a median follow-up of 46.8 months, PFS and response durations were statistically longer in patients in first line (not reached) (figures 1, 2) and was 79 months in pretreated patients. The overall survival rate was 79% at 3 years. As previously reported, delayed responses was observed in 25 patients with a median time of 10.8 months (3.5-26.5) after treatment discontinuation.

The safety of nucleoside analogues has been the subject of investigation in several studies. The principal toxicity of purine analogues is myelosuppression. Long lasting cytopenia was described in one third of patients treated with FCR. For patients in whom high-dose chemotherapy and autologous stem cell transplantation are being considered, nucleoside analogues must be used with precaution. The long term safety of nucleoside analogues (transformation to an aggressive lymphoma, and development of acute myelogenous leukemia/myelodysplasia) will be discussed.

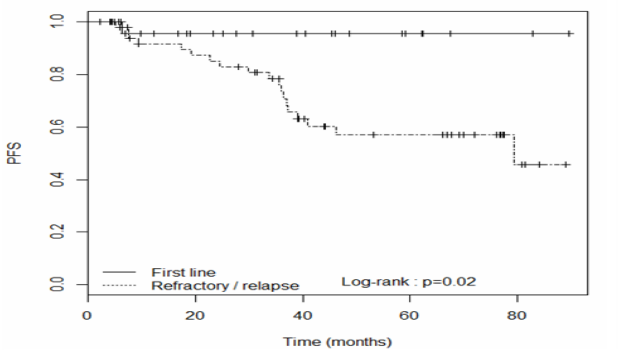

Figure 1

PFS in naïve (n=25) and previously treated (n=57) patients

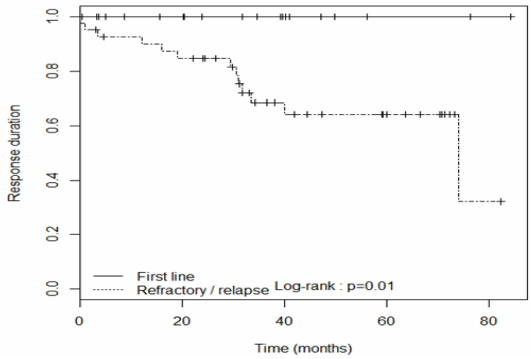

Figure 2

Duration of the response in naive and previously treated patients