Primary Therapy of WM with Nucleoside Analogue Based Therapy

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Both cladribine (2-CDA) and fludarabine (F), alone or in combination, have been extensively evaluated in untreated WM patients. The overall response rate with purine analogues as single agent in previously untreated patients has ranged from 38 to 100%. In a large phase II trial of first-line single-agent F, the overall response rate (ORR) was 38% (CR rate 3%) among 118 patients. The median EFS and OS were 3.0 and 6.8 years respective. In a large randomized study in 168 untreated patients, the ORR was 46% in the F arm, the median progression free survival time was 36 months and the 5-year OS was 69.4%.

Combination therapy with nucleoside analogues has been investigated as both first line and salvage therapy in WM. Laszlo et al recently evaluated the combination of subcutaneous 2-CDA with rituximab (R) in 29 WM patients with either untreated or previously treated disease. With a median follow-up of 65 months, the ORR was 89.6% and the median time to treatment failure (TTF) has not been reached. In a study by the WMCTG, the combination of R and F was administered to 43 WM patients, 32 (75%) of whom were previously untreated. The ORR was 95.3%, and 83% of patients achieved a major response. The median time to progression was 51.2 months. The addition of alkylating agents to nucleoside analogues has also been explored in WM. Weber et al[145] administered two cycles of oral cyclophosphamide (C) along with subcutaneous 2-CDA to 37 patients. At least a partial response was observed in 84% of patients and the median duration of response was 36 months. The FC combination 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.

Weber et al administered R along with 2-CDA and C to 17 previously untreated patients. At least a partial response was documented in 94% of patients including CR in 18%. Tedeschi et al recently completed a multicenter study with FCR by IV route in symptomatic WM patients. The ORR was 89%, with 83% of patients attaining a major remission, and 14% a CR. With a median follow up of 15 months, the median PFS for this study has not been reached. Similar results were observed in 62 patients treated by FCR by oral route. In this retrospective study, the ORR was 85.5%, with 30% of patients attaining a major remission. With a median follow up of 45 months, the median PFS for this study has not been reached and the PFS rate was 65% at 60 months.

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.