

Nucleoside analogue therapy: Balancing Risk and Benefit

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Nucleoside analogues (NAs) have been extensively used for the treatment of low-grade lymphoproliferative disorders and can induce durable responses in Waldenström macroglobulinemia (WM). Cladribine monotherapy, intravenous or subcutaneous, resulted in major responses in 40-90% of untreated WM patients, and 38-54% in the salvage setting. Superimposable results have been obtained with fludarabine at conventional dose. A response rate (RR) ranging from 30% to 40% has been observed in relapsed/refractory WM. In a randomized study, fludarabine as a single agent was superior in terms of RR (30% vs 11%) and response duration (19 vs 3 months) to the combination cyclophosphamide/doxorubicin/prednisone. In first line treatment, fludarabine determined responses from 38% to 100%. The addition of alkylating agents to NAs increases RR (55% in pre-treated, 89% in untreated) and ameliorates the quality of response.

Rituximab (R) has been successfully associated with NAs alone or NAs combined with alkylating agents: a major RR of 86% (CR 4.6%) with a median time to progression prolonged to 51.2 months has been obtained in untreated patients by Treon et al (ASH 2008) with the fludarabine/rituximab (FR) regimen; the combination fludarabine, cyclophosphamide and rituximab (FCR) proved to be active with 83% major RR (Tedeschi et al, ASH 2008).

Myelosuppression and immunosuppression, especially of T cells, are the main source of adverse events after NAs treatment, determining an increased risk of infections. The long term safety of NAs in WM has been examined by Leleu et al (JCO 2008) in a large series. A 7-fold increase in transformation to an aggressive lymphoma or myelodysplastic syndrome (MDS) was observed among patients who received NAs versus other therapies. Treon et al. (ASH 2008), in 43 patients treated with FR observed the development of 3 aggressive lymphomas and 3 MDS/AML (after a median follow-up of 40 mos).

In conclusion, NAs are effective in WM patients. The combination of FC ± R increases response rate and quality of response. It may be an appropriate approach for salvage therapy. On the basis of studies reporting a potential stem cell damage and an increased incidence of transformation to high-grade lymphoma or MDS/AML, NA-based treatments should be avoided in younger patients. Studies are needed to establish the optimal duration of NAs treatment, to reduce immunosuppression related complications and the risk of aggressive lymphoma or MDS.