

[ABSTRACT WM2.2]

ROLE OF PURINE ANALOGS IN FRONT-LINE TREATMENT OF WALDENSTROM'S MACROGLOBULINEMIA

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Waldenstrom's macroglobulinemia (WM), a rare B-cell malignancy, is incurable. Therapy is currently reserved for symptomatic patients. Conventional treatment consists of alkylating agents (especially chlorambucil), with or without steroids.¹ This treatment gives response rates of about 60% and a median survival time of about 60 months. There is increasing evidence that fludarabine (a fluorinated nucleotide analog of the antiviral agent vidarabine) and cladribine (2-chlorodeoxyadenosine, 2-CdA), purine analogs active in low-grade lymphoid malignancies such as chronic lymphocytic leukemia and low-grade lymphomas, are also active in WM resistant to alkylating agents.^{2, 3} There is also evidence that purine analogs may yield higher response rates when used as first-line therapy. Most clinical trials in WM are small phase II studies with widely differing inclusion criteria and response criteria. At the 3rd workshop on WM, held in 2004, it was agreed that alkylating agents, purine analogs and rituximab were reasonable choices for first-line therapy, that there were no data from prospective studies to prefer one agent over another, and that cladribine and fludarabine have the same efficacy. Combinations of alkylating agents, purine analogs and rituximab should now be tested in prospective randomized trials for their efficacy and toxicity relative to single-agent therapy.³

Purine analog monotherapy

Reported response rates to first-line fludarabine therapy range from 38% to 100% (Table 1). In a phase II trial involving 118 untreated patients with WM, the overall response rate to fludarabine monotherapy was 38% (with complete remissions in 3% of patients) after four cycles of 30 mg/m² IV daily for 5 consecutive days, followed by a further four cycles in patients who responded.⁴ Most responses occurred within 3 to 6 months of treatment initiation, but 17% and 5% of responses occurred after more than 6 and 12 months, respectively. The 5-year rates of overall survival (OS) and progression-free survival (PFS) were 62% and 49%, respectively. A serum IgM level below 40 g/L and a β -2 microglobulin level of 3 mg/L or more were the only significant predictors of OS. Only the beta-2 microglobulin level was a significant predictor of PFS. The difference in the response rates between the SWOG study and the other cited studies could be due to the small size of the latter and to differences in patient characteristics and response criteria. In smaller series testing cladribine and pentostatin (Table 2) given as a continuous infusion, bolus injection or subcutaneously, the response rate ranged from 55% to 100% and the responses lasted a median of 13 to 41 months.

Purine analog combinations

Purine analogs have yielded higher response rates when combined with cyclophosphamide in small series, with or without rituximab.

Toxicity of purine analogs

The principal adverse effect of purine analogs is bone marrow suppression, with 30% of patients developing grade 3 neutropenia.⁶ Nucleoside analogs must be used with care in patients being considered for high-dose chemotherapy and autologous stem cell transplantation. Several reports show that peripheral blood stem cell (PBSC) collection at steady state can fail in patients with a history of fludarabine exposure.⁷ In contrast,

PBSC collection can succeed after intermediate-dose Ara-C.⁸ The use of agents that damage stem cells is questionable when high-dose chemotherapy and autologous stem cell transplantation are being considered. Purine analogs lead to a sustained reduction in monocytes and T cell counts (both CD4+ and CD8+), thereby impairing cell-mediated immunity and substantially increasing the risk of opportunistic infections.⁶ Myelodysplasia has been reported to occur with a crude incidence rate of 3.5-8% after fludarabine-containing therapy. Bowcock *et al.* reported a crude incidence rate of 20% in elderly patients, which could be related to fludarabine dose, and adding cyclophosphamide might enhance this risk.⁹ Long-term follow-up of WM patients treated with these agents is needed to assess this risk more precisely. In conclusion, purine analogs are active in both treated and untreated patients with Waldenström's macroglobulinemia. However, there is no consensus on the optimal duration of treatment, and the response rate to first-line purine analog therapy is controversial. Nucleoside analogs, which induce rapid cytoreduction, may be the treatment of choice for patients with serious complications such as hyperviscosity, pancytopenia, and severe peripheral neuropathy. Fludarabine is currently being compared with chlorambucil as primary treatment for WM in a prospective randomized trial.¹⁰

References

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