Multiple Myeloma

The activity and toxicity of low dose clofarabine against relapsed or refractory myeloma

Eight patients with refractory multiple myeloma were treated with clofarabine 4 mg/m²/day on days 1-5 of a 28 day cycle. No objective evidence of anti-myeloma activity was observed (median time to progression of 52 days). All patients experienced grade 3-4 neutropenia and a greater than 50% decrease in platelet counts during treatment.

Clofarabine (2-chloro-2’-fluoro-deoxy-9-β-D-arabinofuranosyladenine, Clofar®, Evoltra®) is a second-generation purine nucleoside analog structurally related to fludarabine and cladribine. In phase 1 and 2 studies of clofarabine, disease activity was observed in acute myeloid and lymphoid leukemias as well as in chronic lymphocytic leukemia. In vitro, clofarabine is cytotoxic against U266 and RPMI 8226 myeloma cell lines at micromolar concentrations. To explore its potential anti-myeloma activity, we conducted a pilot study of clofarabine in patients with relapsed or refractory myeloma.

Patients with relapsed or refractory multiple myeloma with measurable levels of monoclonal protein in serum (≥0.5 g/dL) or urine (≥0.2 g/24 hrs), good performance status (ECOG 0-1), and acceptable organ function (hemoglobin ≥8 g/dL; absolute neutrophil count ≥1,000/mm³; platelets ≥50,000/mm³; aspartate and alanine transaminases, total bilirubin ≤2.5 and creatinine ≤2 x upper limit of normal) were eligible for this study.

Clofarabine 4 mg/m²/day was administered as a 1-hour intravenous infusion on days 1-5 of a 28-day cycle. Response to therapy was evaluated after every cycle using the criteria of Bladé et al. with treatment continued until disease progression or unacceptable toxicity. For patients experiencing grade ≥3 neutropenia or thrombocytopenia, treatment was delayed until count recovery with a dose reduction in subsequent cycles to 2 mg/m²/day. This protocol was approved by the institutional review board of Washington University School of Medicine with all patients providing written informed consent prior to enrollment.

The study population consisted of eight patients with Durie-Salmon stage II or III disease treated with a median of 3.5 (range 2-6) previous anti-myeloma regimens. (Table 1). All had undergone previous autologous stem cell transplant. Patients received a median of two cycles (range 1-5). No objective responses or evidence of anti-myeloma activity was observed as no patient experienced a reduction in monoclonal protein level of >0.1 g/dL. The median time to progression was 52 days (range 24-162).

Adverse events consisted primarily of hematologic toxicity and included grade 3-4 neutropenia in all eight patients and grade 3-4 thrombocytopenia in three patients. However, all eight patients experienced a >50% decrease in platelet counts compared to baseline levels. Interestingly, the timing of cytopenias was discordant. While the platelet count nadir occurred on day 15 of treatment with count recovery by day 28 of each cycle, neutrophil counts had an initial nadir around day 8 of therapy and a second nadir between days 22-28 of therapy with recovery occurring between days 35-42. All patients receiving a second cycle of therapy required dose delay and reduction to 2 mg/m²/day. Despite the severity of the cytopenias, no neutropenic fever or bleeding complication was observed. In addition, no grade 3-4 non-hematologic toxicities were observed.

In addition to its approved indication in pediatric acute lymphoblastic leukemia, clofarabine is currently being tested in clinical trials as a single agent in myelodysplastic syndromes, non-Hodgkin’s lymphoma, chronic lymphocytic leukemia and as a component of multi-agent regimens in acute leukemias. This study reports the first experience of clofarabine in multiple myeloma. Previous trials of structurally related purine analogs, fludarabine and cladribine, failed to demonstrate any disease activity in multiple myeloma. While preclinical evidence suggested that clofarabine may have greater anti-myeloma activity than other purine analogs, we did not observe any evidence of activity at the dose of 4 mg/m²/day for 5 days. Although this study was conducted in a limited number of heavily pretreated patients, the lack of effect on monoclonal protein levels suggest that clofarabine is unlikely to be active against multiple myeloma.

This study also reports the toxicity profile of low-dose clofarabine with prolonged dose-limiting myelosuppression at 4 mg/m²/day. In acute leukemia, reversible severe hepatotoxicity is dose-limiting with a clofarabine dose of 40 mg/m²/day for 5 days, the suggested dose for phase 2 adult acute leukemia studies. While grade 3-4 cytopenias may be acceptable in myeloid malignancies, they are not in low grade lymphoproliferative disorders. The reasons for the discordant timing of cytopenias and the biphasic nature of the neutropenia observed in this study cannot be explained based on the known pharmacokinetic profile of the drug. Future studies of clofarabine in solid tumors or

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low grade lymphoproliferative disorders will likely require doses less than 4 mg/m²/day or longer dosing intervals. Alternatively, once weekly dosing may allow increased dose delivery of clofarabine while avoiding significant dose-limiting myelosuppression.

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References