Enhanced Safety and Tolerability of Dose Intensive Pentostatin and Rituximab in Patients with CLL or Low-Grade B-Cell NHL.

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Abstract

Background

Recent studies have suggested that combination chemotherapy with a purine analog and a monoclonal antibody may have additive as well as synergistic activity in the treatment of NHL and CLL. The first immunochemotherapeutic regimen combined fludarabine (F) and rituximab (R). Although it was efficacious, it was also myelotoxic and immunosuppressive. This multicenter Phase II trial investigated the efficacy and safety of another purine analog, pentostatin (P), in combination with R in the treatment of NHL and CLL patients. (Some of this data has been presented at the 2005 Pan-Pacific Lymphoma Conference).

Methods

One hundred forty-seven patients were enrolled in this study. Eligibility criteria allowed previously treated (PT) and treatment naïve (UT) patients diagnosed with low-grade NHL (REAL classification) or stage II, III, or IV CLL (mod. Rai staging). Treatment consisted of intravenous infusions of R (375 mg/m^2) on day 1 and R (375 mg/m^2) plus dose intensive P (4 mg/m^2) on days 8, 15, 22, 36, 43, and 50, completing 1 cycle. Clinical evaluation was performed after 60 days. If complete response or progressive disease was documented, the treatment was stopped. All other patients were eligible to then receive cycle 2. Patients were stratified by disease and by prior treatment status.

Results

One hundred thirty three patients were eligible for evaluation. One hundred sixty six cycles were administered. Response rate (RR) for NHL-PT was 51% and for NHL-UT was 78%. RR for CLL-PT was 34% and for CLL-UT 42%. There were 30 NHL patients eligible for cycle 2 and 22 went on to receive the additional cycle. Ten patients (45%) achieved an improved objective response. Seventeen CLL patients were eligible for cycle 2 and 8 completed cycle 2. There were 2 (25%) patients that achieved an improved objective response. Median duration of response (DoR) was 11.7, 21.5, 11.9, and 23.7 months, respectively. Median progression-free survival (PFS) was 14.8, 23.5, 13.9, and 25.6 months, respectively. There was a single case of grade 4 neutropenia in each of the PT and UT groups. Overall, neutropenia was the most common adverse event (AE) (6%) in the PT group and was the most common hematological AE (7%) in the UT group. Four patients died within 30 days of receiving chemotherapy (age range 64–88). Causes of death were respiratory insufficiency (2), MI/CAD, and sepsis/CLL.

Conclusions

This immunochemotherapeutic regimen of P+R is active in previously untreated and treated patients with indolent NHL or stage II–IV CLL. The objective response can be improved with prolonged therapy. With only 2/133 evaluable patients experiencing Gr 4 neutropenia, we have demonstrated that this dose intensive regimen was very safe and well tolerated. Future trials comparing the tolerability and efficacy of P+R in combination with cyclophosphamide and/or mitoxantrone to other standard regimens are warranted. The use of combination therapy in elderly patients should be used with caution due to associated co-morbidities.