Novel, effective therapies are needed for peripheral T-cell non-Hodgkin’s lymphoma (PTCL). We treated 16 patients with a combination of gemcitabine, cisplatin and methylprednisolone (GEM-P). Three patients (19%) achieved a complete remission and eight (50%) a partial remission. GEM-P has encouraging efficacy with an acceptable toxicity profile in patients with PTCL.

Peripheral T-cell lymphoma (PTCL) is a heterogeneous disorder comprising several subtypes. Patients with PTCL are often treated similarly to patients with aggressive B-cell non-Hodgkin’s lymphoma but generally the clinical outcome of patients with PTCL is poorer. The relapse rate in patients with PTCL is high and there is currently no accepted standard treatment when patients relapse.

There are few published data evaluating gemcitabine combinations for PTCL. We evaluated the role of gemcitabine (1 g/m² days 1, 8 and 15), cisplatin (100 mg/m² day 15) and methylprednisolone (1 g days 1-5) (GEM-P) repeated every 28 days in a cohort of patients with relapsed/refractory PTCL. Sixteen patients with PTCL were treated at our institution with GEM-P between June 2001 and March 2005 and their records were retrospectively analyzed. Tumor response was measured according to the International Workshop Response Criteria for Non-Hodgkin’s Lymphoma. Toxicity was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0).

Sixteen patients with PTCL were analyzed. The patient’s characteristics, response to treatment and toxicities are presented in Table 1. Histological subtypes were: angioimmunoblastic T-cell lymphoma (n=5), T-cell enteropathy (n=2), NK/T-cell nasal-type (n=2), T-cell anaplastic (ATCL) (n=3), peripheral T-cell lymphoma unspecified (n=2), adult T-cell lymphoma/leukemia associated with human T-cell lymphotrophic virus (HTLV-1) (n=1) and primary cutaneous ATCL (n=1). Median age was 55 years (range: 18-71 years), 69% had an International Prognostic Index score (IPI-score) >2 and 69% had stage III/IV disease.

Fifteen of the sixteen patients were pre-treated. Of 16 evaluable patients, three pts (19%) achieved complete remission (CR), eight pts (50%) achieved partial remission (PR), (ORR=69%; CI-95%: 41.4-89.0) and five patients (31%) progressed while on GEM-P. After a median follow-up of 17.4 months the median time to progression of disease was 123 days (95% CI: 0-288) and the median overall survival (OS) has not been reached. The survival probability at 1 year was 68.2% (95%-CI: 40-85). The main grade 3/4 toxicities were myelosuppression (leukopenia 62%, neutropenia 62% and anemia 12%).

Currently available treatment strategies for PTCL are relatively ineffective; novel therapies are urgently required to improve outcomes for patients with this disease. New approaches including monoclonal antibodies have been investigated with evidence of efficacy as well as toxicity. Targeting different T-cell antigens (CD 52: alemtuzumab; CD25: daclizumab; CD30: SGN 30) has
resulted in tumor response with overall response rates between 36-56%. One trial has also investigated the combination of the CD52-antibody, alemtuzumab, with chemotherapy (fludarabine, cyclophosphamide and doxorubicin). In this study the overall response rate was 61%. Of concern were the grade 3/4 leukopenia that occurred in 81% of the patients and the cytomegalovirus (CMV) reactivation that occurred in 56% of the patients.

In phase II studies, gemcitabine monotherapy has shown activity against T-cell lymphomas involving the skin. Zinzani et al. reported a 70% response rate in a phase II study of 44 pretreated patients with mycosis fungoides or cutaneous PTCL-unspecified. In a further phase II study of 32 previously untreated patients with cutaneous T-cell lymphoma, a 75% response rate to gemcitabine monotherapy was observed, with 22% of the patients achieving a CR. Recently published report on 26 patients with PTCL evaluated the feasibility of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy in patients with PTCL. In this trial an OS rate of 77% was achieved. The median survival was not reached, while the median event-free survival was 7 months at a median follow-up of 12.6 months. The estimated OS at 1 year was 69.6%. Generally the treatment was well tolerated with grade 4 neutropenia occurring in 14 patients (53.8%) and febrile neutropenia in four patients (15.4%).

However, there are very few data available describing the efficacy of gemcitabine combinations in patients with T-cell lymphoma. Emmanouilides et al. evaluated fixed-infusion rate gemcitabine combined with cisplatin and dexamethasone in a cohort of lymphoma patients with mixed histology including five patients with T-cell lymphoma. Two of the five evaluable patients with T-cell lymphoma responded to therapy. The results of our previously reported study were also promising for the subgroup of patients with T-cell lymphoma who received GEM-P chemotherapy (three CR and three PR).

Based on the encouraging results of GEM-P in patients with non-Hodgkin’s lymphoma we analyzed a cohort of patients with a range of T-cell lymphoma histologies who had received the gemcitabine-containing regimen, GEM-P. We observed encouraging responses across the spectrum of diseases, including cutaneous and non-cutaneous T-cell lymphoma. Promisingly consistent responses were seen in patients with T-cell enteropathy or angioimmunoblastic histologies. While the outcome of angioimmunoblastic T-cell lymphoma (AITL) is historically poor with an estimated median survival of less than 3 years, our analysis showed clear evidence of activity of GEM-P in this T-cell entity. Four out of five patients with AILT responded to GEM-P treatment with a median response duration of 8.9 months.

This retrospective analysis has shown that GEM-P has encouraging efficacy for patients with poor prognosis PTCL. The clinical activity, manageable toxicity profile and convenient administration schedule make GEM-P an attractive combination to be investigated in future prospective studies. GEM-P may also be a suitable platform for the addition of targeted therapies. Because of the inherent heterogeneity of PTCL, larger prospective trials, stratified by histological and/or molecular characteristics, will be required to better understand the biology and therapy of PTCL.

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