Gemcitabine, cisplatin and methylprednisolone for the treatment of patients with peripheral T-cell lymphoma: the Royal Marsden Hospital experience

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.

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Peripheral T-cell lymphoma (PTCL) is a heterogeneous disorder comprising several subtypes.[1] 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.[2] 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% C.I.: 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

Table 1. Patients and tumor characteristics.

Pt	*Diagnosis*	*Gender*	*Age*	*Stage*	*IPI*	*1st line treatment*	*Disease Status*	*RR*	*OS (days)*	*Toxicity Grade 3/4*
1	AILT	M	55	3	2	Pmit CEBOM	1st relapse	CR	1143	Neutropenic sepsis, anemia
2	AILT	M	46	4	3	CHOP	1st relapse refractory	PR	295	Neutropenia
3	AILT	M	65	3	2	R-GEM-P	new	CR	270	Neutropenia
4	AILT	M	40	3	2	Pmit CEBOM	2nd relapse	PR	486	Neutropenic sepsis
5	AILT	M	54	4	3	FC	2nd relapse	PD	15	Neutropenia, Alkaline phosphatase
6	T-NHL enteropathy	M	60	4		CHOP	1st relapse refractory	CR	99	
7	T-NHL enteropathy	F	59	1	1	surgery	1st relapse	PR	572	Neutropenic sepsis, anemia
8	ATCL (alk+)	M	19	4	3	Pmit CEBOM	1st relapse	PR	935	Neutropenia
9	ATCL (alk-)	F	31	3	2	Pmit CEBOM	1st relapse refractory	PR	418	Neutropenia
10	ATCL (alk-)	M	71	4	4	Pmit CEBOM	Primary refractory	PR	91	
11	PCATCL	F	37	1	0	CHOP	4th relapse	PR	1058	
12	T/NK-Nasal	F	18	1	1	ProMACECytaBOM + 50 Gy IFRT	1st relapse	PR	868	Neutropenia
13	T/NK-Nasal	F	37	2	1	CHOP	Primary refractory	PD	253	
14	PTCL unspecified	F	70	4	4	Pmit CEBOM	1st relapse	PD	33	Neutropenia
15	PTCL unspecified	M	67	1	2	PCEGemBOM	1st relapse	PD	46	Neutropenia, Bilirubin
16	ATLL (HTLV-1+ve)	F	61	4	3	CHOP Dacluzimab	Primary refractory	PD	110	

AILT: angioimmunoblastic T-cell lymphoma; ATCL alk +/-: anaplastic T-cell lymphoma anaplastic lymphoma kinase +/-; PCATCL: primary cutaneous ATCL; T/NK-nasal: extranodal natural killer T-cell lymphoma nasal type; PTCL unspecified: peripheral T-cell lymphoma, unspecified; ATLL HTLV-1+ve: adult T-cell leukemia/lymphoma with human T-cell lymphotrophic virus. IPI: International Prognostic Index; RR: response; CR: complete remission; PR: partial remission; SD: stable disease; OS: overall survival; PmitCEBOM: prednisolone, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate; ProMACECytaBOM: methotrexate, etoposide, doxorubicin, cyclophosphamide, leucoprolen, bleomycin, vincristine, cytarabine; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; FC: fludarabine, cyclophosphamide; PCGemBO: prednisolone, cyclophosphamide, gemcitabine, bleomycin, vincristine.

resulted in tumor response with overall response rates between 36-56%.[3,4] 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.[5]

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.[6] 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.[7] A 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%).[8]

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.[9] 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).[10]

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 lymphomas. Promisingly consistent responses were seen in patients with T-cell enteropathy or angioimmunoblastic histologies. While the outcome of angioimmunoblastic T-cell lymphoma (AILT) 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.

Hendrik-Tobias Arkenau, Geoff Chong,* David Cunningham,* David Watkins,* Bhawna Sirohi,* Ian Chau,* Andrew Wotherspoon,° Andy Norman,# Alan Horwich,@ Estella Matutes^*

**Department of Medicine, Royal Marsden Hospital, London and Sutton; °Department of Histopathology, Royal Marsden Hospital, London; #Department of Computing, Royal Marsden Hospital, Sutton; @Department of Clinical Oncology, Royal Marsden Hospital, Sutton; ^Department of Hematology, Royal Marsden Hospital, Sutton, UK*

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Correspondence: David Cunningham, Department of Medicine, Royal Marsden Hospital, Downs Road, M2 5PT Sutton, Surrey, United Kingdom. Phone: international +44.0207.3528171 Fax: international +44.0208.6939414. E-mail: david.cunningham@rmh.nhs.uk

References

1. Weidmann E, Gramatzki M, Wilhelm M, Mitrou PS. Diagnosis and actual strategies in peripheral T-cell lymphomas: summary of an international meeting. Ann Oncol 2004; 15:369-74.
2. Cheng AL, Chen YC, Wang CH, Su IJ, Hsieh HC, Chang JY, et al. Direct comparison of peripheral T-cell lymphoma with diffuse B-cell lymphoma of comparable histological grades- should peripheral T-cell lymphoma be considered separately? J Clin Oncol 1989; 7:725-31.
3. Grigg A. Daclizumab in anaplastic large cell lymphoma. Leuk Lymphoma 2006;47:175.
4. Cerveny CG, Law CL, McCormick RS, Lenox JS, Hamblett KJ, Westendorf LE, et al. Signaling via the anti-CD30 mAb SGN-30 sensitizes Hodgkin's disease cells to conventional chemotherapeutics. Leukemia 2005; 19:1648-55.
5. Weidmann E, Hess G, Krause SW. Combination chemoimmunotherapy using alemtuzumab, fludarabine, cyclophosphamide and doxorubicin is an effective first-line regimen in peripheral T-cell lymphoma. Blood 2004; 104:2640[Abstract].
6. Zinzani PL, Baliva G, Magagnoli M, Bendandi M, Modugno G, Gherlinzoni F, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol 2000;18:2603-6.
7. Marchi E, Alinari L, Tani M, Stefoni V, Pimpinelli N, Berti E, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. Cancer 2005;104:2437-41.
8. Kim JG, Sohn KS, Chae YS, et al. CHOP plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy for patients with peripheral T cell lymphomas. Cancer Chemother Pharmacol 2006;58:35-9.
9. Emmanouilides C, Colovos C, Pinter-Brown L, Hernandez L, Schiller G, Territo M, et al. Pilot study of fixed-infusion rate gemcitabine with Cisplatin and dexamethasone in patients with relapsed or refractory lymphoma. Clin Lymphoma 2004;5:45-9.
10. Ng M, Waters J, Cunningham D, Chau I, Horwich A, Hill M, et al. Gemcitabine, cisplatin and methylprednisolone (GEM-P) is an effective salvage regimen in patients with relapsed and refractory lymphoma. Br J Cancer 2005; 92:1352-7.