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Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome

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Background: Peripheral T-cell lymphoma unspecified (PTCLU) and mycosis fungoides (MF) often show resistance to conventional chemotherapy. Gemcitabine should be considered a suitable option. We report the long-term update of 39 pretreated T-cell lymphoma patients treated with gemcitabine.

Patients and methods: From May 1997 to September 2007, 39 pretreated MF and PTCLU patients received gemcitabine. Inclusion criteria were as follows: histologic diagnosis of MF or PTCLU; relapsed/refractory disease; age ≥18 years; and World Health Organization performance status of two or less. Nineteen patients had MF and 20 PTCLU. All patients with MF had a T3–T4, N0, and M0 disease and patients with PTCLU had stage III–IV disease. Gemcitabine was given on days 1, 8, and 15 on a 28-day schedule (1200 mg/m^2/day) for a total of three to six cycles.

Results: Overall response rate was 51% (20 of 39 patients); complete response (CR) and partial response (PR) rates were 23% (9 of 39 patients) and 28% (11 of 39 patients), respectively. Patients with MF had a CR rate of 16% and a PR rate of 32% compared with a CR rate of 30% and a PR rate of 25% of PTCLU patients. Among the CR patients, 7 of 9 are in continuous complete response with a variable disease-free interval (15–120 months).

Conclusion: In our experience, gemcitabine proved to be effective in pretreated MF and PTCLU patients, even in the long term.

Key words: chemotherapy, gemcitabine, mycosis fungoides, peripheral T-cell lymphomas, radiotherapy

introduction

The results of treatment of patients with aggressive T-cell lymphomas are generally worse than those for patients with diffuse large B-cell lymphomas [1–3]. In particular, most aggressive peripheral T-cell lymphoma unspecified (PTCLU) patients are traditionally treated with an anthracycline-containing regimen and complete response (CR; CR requires the complete disappearance of all detectable clinical and radiographic evidence of disease, the disappearance of all disease-related symptoms, and normalization of biochemical abnormalities) rates of 50%–70% have been reported [4–6]. However, the 5-year overall survival for PTCLU patients was 20%–30%. This did not significantly differ by the type of chemotherapy administered. The effects of high-dose therapy and stem-cell transplantation at the time of first CR were not easily evaluated due to difficult comparisons; however, stem-cell transplant at the time of relapse did offer an advantage over salvage chemotherapy.

Regarding the cutaneous T-cell lymphoma and in particular mycosis fungoides (MF), the use of systemic chemotherapy as a first-line treatment should be restricted with few exceptions to advanced/aggressive MF patients [7–9]. The choice of treatment is often determined by institutional experience, particularly as there is a paucity of data from phase III trials and a lack of consensus concerning treatment of the later stages of MF. A strict rule is definitely nonappropriate in this regards; a careful and balanced evaluation of specific diagnosis, tumor load, cutaneous lesions' features, age, general conditions, and immune status of the patients is obviously the standard to date.

Among the several second-line and experimental drugs, gemcitabine should be considered one of the most suitable options to date for pretreated PTCLU and MF patients. Gemcitabine has been demonstrated to be an effective monotherapy with a 60%–70% overall response rate (ORR) in patients with advanced disease and heavily pretreated [10–13]. In addition, there are also interesting data in untreated patients [14] and even some data describing the efficacy of gemcitabine combinations in patients with T-cell lymphoma [15–18].

As well known, it is difficult to find in literature the long-term outcome regarding the efficacy of a single-agent drug in pretreated patients and, in particular, in rare diseases such as T-cell lymphomas. In this study, we report the long-term update of the outcome of 39 heavily pretreated T-cell lymphoma patients after salvage treatment with gemcitabine.

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patients and methods

From May 1997 to September 2007, after their informed consent, 39 patients with previously treated MF and PTCLU completed treatment with gemcitabine at the Institute of Hematology and Medical Oncology 'L. e A. Seràgnoli'. Inclusion criteria included the following: histologic (with immunohistochemistry) diagnosis of MF or PTCLU according to the Revised European-American Lymphoma classification [19]; relapsed or refractory disease after at least two conventional therapeutic approaches (chemotherapy and/or radiotherapy); age ≥18 years; and World Health Organization (WHO) performance status of two or less.

The extent of the disease was determined before and at the end of the treatment, as well as during the follow-up, by complete skin examination, physical examination, laboratory tests, computed tomography (CT) scanning of the chest, abdomen, and pelvis and bone marrow biopsy (it was repeated at the end of the treatment only if it was positive at baseline).

patient population

Detailed patient characteristics are listed in Table 1. Nineteen of 39 patients had a diagnosis of MF and 20 of PTCLU. All patients with MF were classified with T3 or T4, N0, and M0 disease [20] using the tumor–node–metastasis classification for T-cell lymphomas and patients with PTCLU were classified with stage III–IV disease according to the Ann Arbor staging system [21]. The median age of the patients was 54 years (range 32–78 years); 29 patients were male and 10 were female. The median number of prior treatments was three (range 2–8).

treatment protocol

Gemcitabine hydrochloride (Gemzar; Eli Lilly, Indianapolis, IN) was supplied as a lyophilized powder. The drug was diluted in normal saline solution and administered i.v. over 30 min. Gemcitabine was given to all patients on days 1, 8, and 15 of a 28-day schedule at a dose of 1200 mg/m^2 per day for a total of three to six cycles (8 patients had three courses, 2 patients had four courses, and 20 patients underwent upto six courses). All cycles were delivered on an outpatient basis.

response evaluation

Tumor response was assessed by measuring the reduction in skin lesions on physical examination and the reduction in lymph node infiltration by CT scan. Response was defined according to previously reported international criteria [22].

Table 1. Clinical characteristics of 39 patients

MF/PTCLU, number of patients	19/20
Age, years	
Median	54
Range	32–78
Sex male/female ratio	29/10
Previous treatments, *n*	
Median	3
Range	2–8
TNM classification/Ann Arbor stage	
MF (T3 or T4)	19
PTCLU	
Stage III–IV	12
IV skin	8

IV skin: Stage IV disease with peculiar involvement of the skin.
MF, mycosis fungoides; PTCLU, peripheral T-cell lymphoma unspecified; TNM, tumor–node–metastasis.

Patients were evaluated by weekly history and physical examinations, complete blood counts, and chemistry profiles. All signs, symptoms, or laboratory abnormalities were assessed using WHO criteria for toxic effects.

results

response

Clinical results are summarized in Table 2. The ORR [CR + partial response (PR; PR requires a 50% decrease or more in sum of the products of the greatest diameters of the six largest dominant nodes or nodal masses. There should be no increase in the size of the other nodes, liver or spleen)] was 51% (20 of 39 patients); the CR and PR rates were 23% (9 of 39 patients) and 28% (11 of 39 patients), respectively. According to the histologic subtypes, patients with MF had a CR rate of 16% (3 of 19 patients) compared with 30% (6 of 20 patients) of the patients with PTCLU. Patients with MF had a PR rate of 31.5% (6 of 19 patients) compared with 25% (5 of 20 patients) of the patients with PTCLU.

Among the nine CRs, five were histologically confirmed when reevaluated with a local biopsy; seven of these patients (including all histologic CRs) were still in remission with a median time of 34 months (range 15–120 months) from the end of gemcitabine. The other two patients relapsed after 7 and 10 months, respectively. The former was a systemic PTCLU patient who presented a nodal relapse in several sites; the latter was an MF patient who showed a diffuse skin relapse.

Regarding the seven long-term continuous complete responses (CCRs) (Table 3), two patients had MF and five patients had PTCLU (three with systemic disease and with isolated skin involvement). Table 3 summarizes the characteristics of these patients. The Figure 1 explains the algorithm during the outcome of all nine CRs.

treatment toxicity

Gemcitabine was generally well tolerated, and all of the responding patients completed the treatment. With regard to hematologic toxicity, no WHO grade 3–4 was observed. Grade 1–2 neutropenia was reported in 15 (38.5%) patients, and grade 1–2 thrombocytopenia was recorded in 18 (46%) patients; the duration of thrombocytopenia was <2 weeks. Concerning the non-hematologic toxicity, hepatic toxicity (transient increase of liver enzymes) was reported in 14 (36%) patients (in all cases, it was grade 1 or 2, but one patient had grade 3). No patient

Table 2. Response rate of 39 patients

Response	MF (n = 19) Number of patients (%)	PTCLU (n = 20) Number of patients (%)	Total (N = 39) Number of patients (%)
CR	3 (16)	6 (30)	9 (23)
PR	6 (32)	5 (25)	11 (28)
CR + PR	9 (48)	11 (55)	20 (50)

MF, mycosis fungoides; PTCLU, peripheral T-cell lymphoma unspecified; CR, complete response; PR, partial response.

Table 3. Characteristics of seven CCRs

	Sex	Age	Diagnosis	Stage	Previous treatments	Duration of response (months)
1	Female	66	PTCL	III	CHOP; RT; DHAP	15
2	Male	48	MF	IV	PUVA; CVP; Campath; Bexarotene	18
3	Male	50	PTCL	IV_{SKIN}	CHOP; RT	22
4	Male	69	PTCL	III	CHOP; IEV; RT	34
5	Female	68	PTCL	III	RT; CHOP; Campath	43
6	Male	71	PTCL	IV_{SKIN}	CHOP; Campath	60
7	Male	75	MF	IV	PUVA; RT; CVP	120

CCRs, continuous complete responses; PTCL, peripheral T-cell lymphoma; CHOP, combination chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisone; RT, radiotherapy; DHAP, combination chemotherapy with dexamethasone, high-dose aracytin, cisplatin; MF, mycosis fungoides; PUVA, psoralen plus UVA; CVP, combination chemotherapy with cyclophosphamide, vincristine, and prednisone; IEV, combination chemotherapy with ifosfamide, epirubicin, and etoposide.

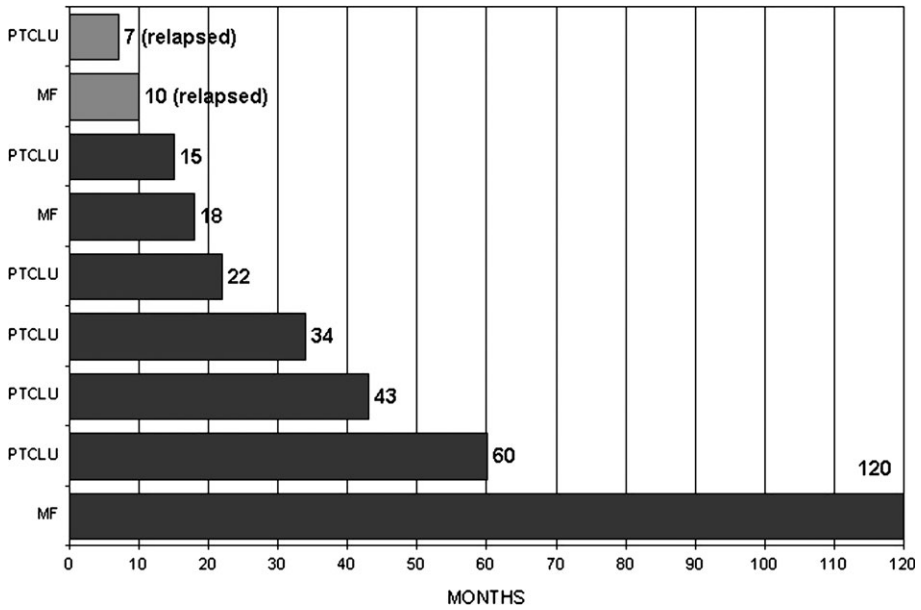

Figure 1. Outcome of nine patients who obtained a complete response and disease-free interval.

experienced complete alopecia, no nausea and emesis was reported, and none of the patients died of complications related to gemcitabine.

discussion

In the last years, many steps forward have been made in the classification and treatment of peripheral T-cell lymphoma and MF. Several initiatives are going on to clearly and distinctly categorize the T-cell lymphomas in order to define appropriate therapies for each disease entity. New studies are required to assess gene expression profiling with comparative genomic hybridization and detailed phenotypic, cytogenetic, and molecular genetic analysis to better understand disease pathogenesis and develop new prognostic models and targeted therapies. Progress expected from genomic and proteomic studies may improve our ability to develop active treatments, which may in turn improve the outcome for patients.

New therapeutic approaches and the incorporation of novel agents into these therapeutic regimens are necessary to improve the outcome of T-cell lymphomas. Gemcitabine is one of the most effective drug in PTCLU and MF; it has been active both as a single agent [10, 14] and in combination with other conventional antiblastic drugs [15–18]. In addition, combination of gemcitabine with a new other compound, pralatrexate, is currently being explored in a phase I/II clinical trial [23].

The addition of the anti-CD20 mAb rituximab to chemotherapy regimens like combination chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisone has significantly improved treatment outcomes in B-cell lymphomas. As such, several mAbs are currently being tested in PTCLU, including alemtuzumab, iratumumab, siplizumab, and zanolimumab [24–27].

There are drugs such as proteasome inhibitors [**28**], histone deacetylase inhibitors [29, 30], and folate analogues [31]

currently being evaluated in clinical trials and their preliminary data have shown promising single-agent activity in MF patients; at the same time, folate analogues showed interesting results on PTCLU [32] in a multicentre phase II trial.

The real problem of several phase II studies with new agents in rare disease like T-cell lymphomas is the update of the preliminary results in terms of duration of the response. This concept can play a pivotal role in improving our ability to develop active multiagent treatments. Our update on the role of gemcitabine as a single agent in pretreated T-cell lymphoma patients lead us to conclude that this drug has a substantial activity with acceptable toxicity and, in particular, it indicates a good quality of the response, since 7 of 39 (18%) patients are CCRs with a median time of 34 months. This post hoc subset analysis provides evidence for the long-term clinical benefit of gemcitabine in heavily pretreated PTCLU and MF, regardless of prior treatment failures.

Further studies will help to establish the clinical significance of these results and elicit the best use of this compound, either as a single agent or in combination with others.

funding

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