Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients.

Gemcitabine as Frontline Treatment for Cutaneous T-Cell Lymphoma

Phase II Study of 32 Patients

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BACKGROUND. Based on the activity of gemcitabine in heavily pretreated patients with cutaneous T-cell lymphoma (CTCL), the objective of the current study was to determine the role of gemcitabine in the treatment of patients with advanced, untreated CTCL.

METHODS. Between June 2002 and February 2004, 32 untreated patients with mycosis fungoides (MF) (n = 26 patients); peripheral T-cell lymphoma, unspecified (PTCLU) with exclusive skin involvement (n = 5 patients); and Sezary syndrome (SS) (n = 1 patient) were enrolled in a 7-institution, Phase II trial and treated with gemcitabine. This drug was given on Days 1, 8, and 15 of a 28-day schedule at a dose of 1200 mg/m^2 intravenously over 30 minutes for a total of 6 cycles.

RESULTS. Of the 32 patients studied, 7 (22%) achieved a complete response (CR) and 17 (53%) achieved a partial response (PR), whereas the remaining 8 patients showed no benefit from the treatment. Five of the CRs were confirmed histologically. The CR and PR rates were found to be the same for patients with MF and PTCLU, respectively. The median duration of CR was 10 months (range, 4–22 mos). Treatment appeared to be well tolerated; hematologic toxicity was mild and no nausea/emesis or organ toxicity was noted.

CONCLUSIONS. The results of the current Phase II study demonstrate the activity of gemcitabine as a single agent in untreated CTCL patients. Further studies using gemcitabine in combination, either contemporary or sequentially, with other drugs in patients with advanced stage, untreated CTCL are needed. ***Cancer* 2005;104: 2437–41.** © *2005 American Cancer Society.*

KEYWORDS: gemcitabine, cutaneous T-cell lymphoma (CTCL), untreated patients.

The term primary cutaneous lymphoma refers to cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. Cutaneous lymphomas are the second most common group of extranodal lymphomas, after gastrointestinal lymphomas.[1,2]

The CTCL spectrum includes mycosis fungoides (MF), which represents approximately 80% of cases; erytrodermic expressions of CTCL, including Sezary syndrome (SS), which represent 10–15% of cases; and a variety of other peripheral T-cell lymphomas that arise in the skin.[3]

The treatment of CTCL has been in a state of continual change over the past few years as new therapies continue to emerge in the search for more effective treatments. However, the prognosis of patients with CTCL remains dependent on their overall clinical stage of disease (Ann Arbor Stage IA-IVBr) at the time of presentation as well as their response to therapy. Past therapies have been limited by

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toxicity or a lack of consistently durable responses, and to our knowledge few treatments to date have been shown to actually alter survival, especially in patients with late-stage disease. Even aggressive chemotherapy has not been shown to improve overall survival.[4]

Patients with disease limited to the skin, in the form of patches and plaques, respond best to "skin direct therapy" with topical agents including corticosteroids, nitrogen mustard, carmustine, and bexarotene in a gel formulation (or, more recently, as an oral formulation), as well as phototherapy with ultraviolet B light, psoralen and ultraviolet A radiation therapy (PUVA), or photodynamic therapy.[5]

Recently approved by the Food and Drug Administration (FDA), denileukin diftitox is the first of a novel class of fusion toxin proteins and is selective for interleukin-2R (CD25+), targeting the malignant T-cell clones in CTCL.[6] More recent developments in the treatment of CTCL include selective immunomodulatory agents and monoclonal antibodies.[7,8]

At the forefront of developing systemic chemotherapy, pegylated liposomal doxorubicin, pentostatin, and gemcitabine appear to have the greatest potential for success in CTCL therapy.[9–14] Gemcitabine (2′,2′-difluorodeoxycytidine) in particular is a pyrimidine antimetabolite with structural similarities to cytarabine; however, its pharmacology and mechanism of action differ from other pyrimidine analogs in several aspects. Gemcitabine serves as a better transport substrate for uptake into the cells, is phosphorylated more efficiently to the active gemcitabine triphosphate, inhibits elongation of the DNA chain through a mechanism termed "masked chain termination," and competitively inhibits ribonucleotidyl reductase. The result is impaired DNA synthesis and the induction of apoptosis.

In the field of hematology, gemcitabine has been demonstrated to be active in heavily pretreated patients with Hodgkin disease,[15,16] as well as those with aggressive and indolent non-Hodgkin lymphoma.[17,18]

The objective of the current study was to determine the role of gemcitabine in previously treated (only local radiotherapy or PUVA therapy) or untreated patients with advanced MF and peripheral T-cell lymphoma, unspecified, with skin involvement (PTCLU).

MATERIALS AND METHODS

Between June 2002 and February 2004, 32 patients with untreated MF, PTCLU, and SS were treated with gemcitabine in 7 Italian institutions. Criteria for inclusion in the study included a histologic diagnosis of MF, SS, or PTCLU according to the Revised European–American Lymphoma (REAL) classification[2]; the presence of measurable lesions; untreated disease or disease previously treated with local radiotherapy or PUVA therapy at least 3 months before enrollment in the protocol; isolated cutaneous involvement and lesions limited to a single (bulky) cutaneous region or disseminated disease, involving at least 2 nonadjacent regions; a performance status of 0–1 according to ECOG score; normal cardiac, renal, and hepatic function; a negative pregnancy test for female patients, and negative serology for the human immunodeficiency virus, hepatitis B virus, and hepatitis C virus.

TABLE 1
Characteristics of the Study Group

Characteristic	
M:F ratio	22:10
Age in yrs	
Median	58
Range	25–77
Histology	
MF	26 (81%)
PTCLU	5 (16%)
SS	1 (3%)
Previous treatments (n = 22 patients)	
Radiotherapy	4
PUVA	10
PUVA plus local radiotherapy	8
TNM classification/Ann Arbor stage	
MF (T3 or T4, N0,M0)	26
PTCLU (Stage IV, skin)	5

M:F: male-to-female; MF: mycosis fungoides; PTCLU: peripheral T-cell lymphoma, unspecified; SS: Sezary syndrome; PUVA: psoralen and ultraviolet A radiation therapy.

Disease extension was determined at the time of diagnosis and at the end of treatment with complete physical examination, including complete skin examination and determination of tumor size; laboratory tests; computed tomography (CT) scanning of the chest, abdomen, and pelvis; and bone marrow biopsy. CT scanning and bone marrow biopsy were repeated at the end of treatment only if they were positive at the time of diagnosis. Response evaluation was performed between 3–5 weeks after the last course of treatment. During each subsequent course of gemcitabine therapy, physical examination, laboratory tests, and grading of acute and subacute toxicity were evaluated and adverse events were determined.

Patient Population

Detailed patient characteristics are listed in Table 1. Twenty-six of 32 patients had a diagnosis of MF, 5 were diagnosed with PTCLU, and only 1 patient had SS. All patients with MF were classified with T3 or T4,

TABLE 2
Treatment Outcome

	Total (n = 32 patients)	MF (n = 26 patients)	PTCLU (n = 5 patients)	SS (n = 1 patient)
CR	7 (22%)	6 (23%)	1 (20%)	—
PR	17 (53%)	13 (50%)	4 (80%)	—
No response	8 (25%)	7 (27%)	—	1 (100%)
CR + PR	24 (75%)	19 (73%)	5 (100%)	—

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

N0, M0 disease[19] using the TNM classification for T-cell lymphoma and patients with PTCLU were classified with Stage IV disease according to the Ann Arbor staging system.[20] The median age of the patients was 58 years (range, 25–77 yrs); 22 patients were male and 10 were female. Of the 32 patients studied, 4 had been previously treated with local radiotherapy, 10 had received previous PUVA therapy, and 8 had been treated previously with PUVA and radiotherapy, whereas 10 patients had not received any previous treatment.

Treatment Protocol

Gemcitabine hydrochloride (Gemzar®; Eli Lilly and Company, Florence, Italy) was diluted in normal saline and administered intravenously over the course of 30 minutes. 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 6 cycles. 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.[21]

Overall survival (OS) and progression-free survival (PFS) curves were calculated according to the method of Kaplan and Meier.[22] Toxicity was evaluated through weekly physical examination, complete blood counts, and chemistry (biochemical) profiles. All signs, symptoms, or laboratory abnormalities were defined using the World Health Organization criteria for toxicity.

RESULTS

Treatment Outcome

Clinical results are summarized in Table 2. The overall response rate (CR + PR) was 75 % (24 of 32 patients). The CR and PR rates were 22% (7 of 32 patients) and 53% (17 of 32 patients), respectively. Patients with MF had a CR rate of 23% (6 of 26 patients) and a PR rate of 50% (13 of 26 patients). Conversely, patients with PTCLU had a CR rate of 20% (1 of 5 patients) and a PR rate of 80% (4 of 5 patients). The one patient with a diagnosis of SS had no response after therapy.

Of the 7 patients who achieved a CR, 3 were still in disease remission after a median follow-up of 10 months (range, 4–22 mos).

Figure 1 shows the PFS curve of all patients who were treated with gemcitabine. The median PFS was 10 months (range, 1–22 mos). Figure 2 shows the OS curve. The median OS was 19 months (range, 8–32 mos).

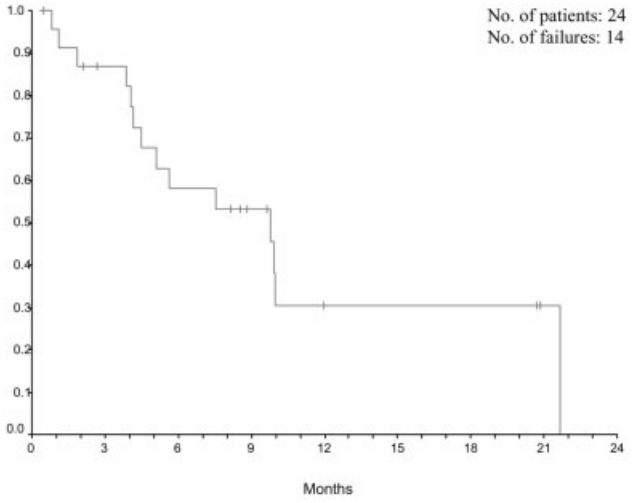

FIGURE 1. Progression-free survival curve of all responding patients.

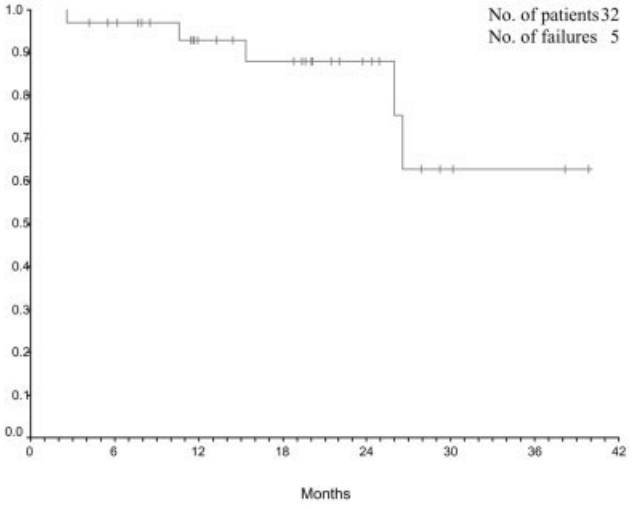

FIGURE 2. Overall survival curve of the entire study population.

Treatment Toxicity

Gemcitabine was generally well tolerated (Table 3). With regard to hematologic toxicity, 37.5% (12 of 32

TABLE 3
Treatment Toxicity

WHO grade	1–2	3	4
Hematologic			
Anemia	12 (37.5%)	1 (3%)	—
Thrombocytopenia	14 (43%)	2 (6%)	2 (6%)
Leukopenia	12 (37.5%)	5 (16%)	—
Nonhematologic			
Neurologic	2 (6%)		
Hepatic	11 (34%)	1 (3%)	1 (3%)
Renal	2 (6%)	—	—
Pulmonary	3 (9%)	—	—
Cardiac	1 (3%)	—	—

WHO: World Health Organization.

patients) had WHO Grade 1-2 anemia and 3% (1 of 32 patients) had WHO Grade 3 anemia. No patients were found to have WHO Grade 4 anemia. Grade 3-4 thrombocytopenia and neutropenia were observed in 12% (4 of 32 patients) and 16% (5 of 32 patients), respectively. With regard to nonhematological toxicity, the most significant toxicity was hepatic toxicity. Grade 1-2-3 hepatic toxicity was observed in 37% of patients (12 of 32 patients) and Grade 4 hepatic toxicity was reported in 3% of patients (1 of 3 patients). However, the hepatic injury was reversible in all cases. Hair loss was mild to moderate, and no patients experienced complete alopecia. No nausea and emesis were reported. There were no instances of renal or cardiac toxicity. No patients died of complications related to gemcitabine.

DISCUSSION

T-cell malignancies are reported to comprise approximately 15% of all hematologic neoplasms diagnosed in Western countries. Although more information concerning the pathobiology and immunology of these tumors has become available, there is considerable debate regarding their clinical behavior and response to conventional treatment. Several authors have reported satisfactory results using purine analogs in the treatment of different types of recurrent or refractory T-cell malignancies.[14,23,24]

Kurzrock et al. reported results using pentostatin in 28 CTCL patients; the overall response rate was 71% and the most common side effects were granulocytopenia, nausea, and nonneutropenic fever.[25] Other studies examining cladribine, fludarabine, and gemcitabine as single agents in pretreated CTCL patients reported an overall response rate of 24–47% for cladribine and fludarabine.[23,24] The most interesting data were obtained for gemcitabine. Sallah et al. reported an overall response rate of 60% with a 20% CR rate; our previous reports demonstrated a 70% overall response rate with a CR rate of 11%.[13,14]

These findings led us to conclude that gemcitabine has the highest activity with acceptable toxicity in previously treated patients with CTCL. For this reason, we decided to use gemcitabine as the frontline treatment of CTCL to evaluate tumor response, as well as the safety and duration of response.

In the current study, we obtained an overall response rate of 75%, with a CR rate of 22% and a PR rate of 53%. Nine of 32 patients had a follow-up period of at least 18 months; at the time of last follow-up, 8 of 9 patients were alive (89%) and 1 patient remained in complete disease remission.

Gemcitabine as a single agent has proven to be effective in untreated patients with CTCL; moreover, its modest toxicity profile and easy schedule of administration make it an ideal agent for frontline use. Recent studies have demonstrated the efficacy and safety of gemcitabine, cisplatin, and steroids in the treatment of patients with recurrent or refractory Hodgkin disease and non-Hodgkin lymphoma.[26,27] Gemcitabine also has been tested in association with oxaliplatin in patients with recurrent and refractory lymphoma.[28] This combination also has been shown to be effective in heavily pretreated patients with T-cell non-Hodgkin lymphoma. In future trials, it will be interesting to test these gemcitabine-containing regimens in patients with CTCL. In particular, based on preliminary data from the study of alemtuzumab in CTCL patients, we currently are planning a Phase II trial in untreated patients, comprised of an initial phase with gemcitabine and a sequential consolidation phase with low-dose alemtuzumab.

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