

Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma

Between July 2003 and March 2004, nine patients with pretreated mycosis fungoides were enrolled into a phase II trial and were treated with temozolomide. The overall response rate was 33%. Further studies are needed to test the efficacy of temozolomide, alone or in combination in earlier stages of this disease.

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Mycosis fungoides (MF) is the most frequent variant of cutaneous T-cell lymphoma. Clinically, MF is typified by the development of patches, plaques or tumors that may be followed by spread to lymph nodes and visceral organs.¹ Standard treatment options are typically palliative. PUVA remains the gold-standard for the treatment of MF stage IA to IIA. Systemic therapies are reserved for more advanced stages including single-agent (fludarabine, 2-deoxycoformycin, gemcitabine) or multiagent therapy (methotrexate, chlorambucil, doxorubicin, etoposide, purine analogs, retinoids, interferon α or γ , recombinant toxins and monoclonal antibody directed against the lymphocyte surface antigen CD52).²⁻⁵

Temozolomide, an imidazotetrazine derivative, is an oral alkylating agent that was developed in view of its demonstrated antitumor activity and safety profile in pre-clinical tests. Temozolomide has excellent oral bioavailability and has shown a promising efficacy in metastatic melanoma, primary brain tumors and MF.^{6,7}

Between July 2003 and January 2004, in a prospective single center phase II study, we administered temozolomide (Schering-Plough, Milan, Italy) to nine heavily pretreated patients with MF, after having received their informed consent in accordance with the ethical policy of the Institute. The study complied with the Helsinki declaration. For the first cycle, patients were treated with 150 mg/m²/day p.o. for 5 consecutive days, whereas for the second and third cycles they were treated with 200 mg/m²/day p.o. for 5 consecutive days; the cycles were repeated every four weeks for a total of three courses.

The patients' characteristics are listed in Table 1. All patients had previously been treated with at least two chemotherapeutic and/or radiotherapeutic approaches (Table 2) and were selected according to strict criteria: isolated cutaneous involvement for at least 6 months, and no evidence of possible disease spread (evaluated by computed tomography of the chest, abdomen and pelvis, and bone marrow aspiration and trephine biopsy). Patients had stage IIB or III disease according to the Tumor-Node-Metastasis classification of cutaneous T-cell lymphoma.⁸ The diagnosis was histologically confirmed according to the REAL classification.⁹

Tumor response was detected by measuring the reduction of skin lesions in all patients. Complete response (CR), partial response (PR), and no response were evaluated according to the international criteria.¹⁰ Patients were evaluated by weekly history taking and physical examination, complete blood counts and chemistry profiles. All signs, symptoms or laboratory abnormalities were assessed using WHO criteria for toxicities. The overall

Table 1. Patients' characteristics at entry into the study.

Total patients	9
Mean age, yrs (range)	59 (46-72)
Sex M/F	7/2
Time from diagnosis (yrs):	
median	5.3
range	1-17
N. of prior treatments:	
median	3
range	2-5

Table 2. Previous treatments in the nine patients treated with temozolomide.

Pt. No.	Previous therapies
1	Interferon- α -2a; Gemcitabine
2	Interferon- α -2a; Gemcitabine
3	PUVA; Interferon- α -2a; Gemcitabine
4	PUVA; CHOP; Gemcitabine
5	VNCOP-B; Radiotherapy; Gemcitabine; Campath-1H
6	Corticosteroids; Radiotherapy; PUVA; Gemcitabine; Roentgen therapy
7	PUVA; Radiotherapy; Gemcitabine
8	PUVA; Gemcitabine; Campath-1H
9	PUVA; Gemcitabine

response rate (CR + PR) was 33% (3 of 9 patients); the CR and PR rates were 11% (1 of 9 patients) and 22% (2 of 9 patients), respectively. Three patients reached stable disease and the remaining three showed no response. All responses occurred after no later than two courses of temozolomide. The follow-up is currently short (median 10 months, range 8-15 months). The patient who achieved a CR had a 2-year history of MF: he had received four prior chemotherapeutic regimens, the last of which had been gemcitabine, without any response. After the therapy, he remained disease-free for 6 months before relapsing. The two patients who achieved PR are still in remission after 8 and 9 months.

In general, temozolomide was extremely well tolerated. All patients received the planned three courses of treatment. No WHO grade 4 hematologic toxicity was observed. A 1-week delay was required for two patients who developed grade 3 thrombocytopenia and grade 3 neutropenia. None of the patients required transfusion or medication with granulocyte colony-stimulating factor.

Drug-related symptomatic toxicity was generally mild: nausea/vomiting were successfully controlled with conventional antiemetic medications. There were no infections. No alopecia was recorded.

The prognosis of MF is generally considered poor.¹ The use of combined treatment modalities should be limited to MF patients with an aggressive course, or to those with extracutaneous manifestations, since studies reveal no difference in long-term remission or survival rate when used at an earlier stage. In advanced stage MF, treatment with chemotherapy is generally recommended, but few patients obtain a long-lasting remission.

The present study shows that temozolomide effectively induced remissions in heavily pretreated MF with a significant overall response rate (33%). The overall response rate of our study is comparable to that reported in the literature on MF patients treated with other single agents.² In addition, all therapy was administered orally, and the associated toxicity was very modest.

Its modest toxicity profile, easy schedule and administration modality make temozolomide an interesting agent for consideration in the development of chemotherapy regimens. These results are encouraging but larger trials will be necessary to further explore the therapeutic potential of temozolomide, alone or in combination, in the treatment of MF and of other types of cutaneous lymphoma.

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