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Short communication

Phase II trial of trimetrexate in patients with advanced soft-tissue sarcoma

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Summary. Trimetrexate, a lipophilic, 2,4-diaminoquinazoline derivative of methotrexate, enters cells by passive diffusion rather than via a transport system. Trimetrexate has shown promising activity in animal model systems. A total of 16 patients with metastatic soft-tissue sarcoma who had received only one prior chemotherapy regimen were treated with trimetrexate (8 mg/m^2 given intravenously daily for 5 days) every 3 weeks. Treatment-related toxicity included ≥ grade 2 neutropenia (8/16), thrombocytopenia (3/16), mucositis (4/16) and skin rash (3/16). No partial or complete responses were observed in 15 evaluable patients (95% confidence interval for true response rate, 0–22%) Six subjects showed stabilization of disease for periods ranging from 2 to 9 months. At this dose and on this schedule, trimetrexate appears to have little activity against refractory soft-tissue sarcomas.

Introduction

Trimetrexate, a 2,4-diaminoquinazoline derivative of methotrexate, is an effective folic acid antagonist. Several differences between trimetrexate and methotrexate renders the former drug of clinical interest. Both compounds inhibit dihydrofolate reductase (DHFR) in the murine lymphoid leukemia cell line L1210 and in human leukemia cells [1]. In L1210 cell lines in which methotrexate resistance is based on deficient transmembrane transport, trimetrexate accumulates intracellularly in proportion to the extracellular concentration, whereas methotrexate accumulation is minimal [2]. Several other methotrexate-resistant cell lines remain trimetrexate-sensitive when transport deficiency is the moderator of methotrexate resistance [5]. Trimetrexate accumulates to a higher extent in human leukemia cells than does methotrexate, probably due to the lipophilic nature of the former [1, 2].

Toxicity and antitumor effects caused by the folic acid antagonists are associated with intracellular drug-related inhibition of DHFR and resultant cytotoxicity. Increased intracellular retention of methotrexate results from the formation of methotrexate polyglutamate complexes [6]. Trimetrexate lacks a glutamic acid residue, which excludes a contribution of this mechanism of folic acid antagonism. Trimetrexate toxicity can be modified by the administration of leucovorin at a dose and in a manner similar to that used to treat methotrexate toxicity. The dose-limiting toxicity of trimetrexate is myelosuppression, with mucositis, rash, and pulmonary toxicity also being reported [4–6, 10]. Initial results from Canada suggested that trimetrexate exhibited activity against soft-tissue sarcomas [9]. Given the modest rate of response of soft-tissue sarcomas to methotrexate [3] a phase II trial of trimetrexate in patients with soft-tissue sarcomas was initiated.

Patients and methods

The eligibility criteria included histologically documented metastatic or inoperable soft-tissue sarcoma (reviewed at Brigham and Women's Hospital); a Cancer and leukemia Group B (CALGB) performance status of 0–2; an age of >18 years; measurable disease on physical examination or radiographs; the completion of one prior chemotherapy regimen; no chemotherapy or radiation therapy in the 4 weeks before the start of treatment; a WBC count of >3,000/μl; a platelet count of >100,000/μl; blood urea nitrogen (BUN) creatinine, bilirubin, and SGOT levels of <1.5 times the normal values, and albumin levels of >3.5 mg/dl. Patients exhibiting pleural effusions were excluded. Informed consent was obtained from each subject and the protocol was approved by the Institutional Review Board of the Dana-Farber Cancer Institute.

Trimetrexate was given at a dose of 8 mg/m^2 by intravenous bolus over a 5 to 10-min period daily for 5 days. Courses were repeated at 21-day intervals if no grade 3–4 toxicity was observed. Subsequent courses of therapy were delayed until the granulocyte count rose to >1,800/μl and the platelet increased to count >100,000/μl. For the second and subsequent courses, if grade 0–1 (CALGB criteria) toxicity was noted during the first or prior course of therapy, the trimetrexate dose was increased by 2 mg/m^2 per day for the next course. The dose remained unchanged in the presence of grade 2 toxicity but was decreased

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Table 1. Patients' characteristics and toxicity

	Patients (*n*)
Characteristics:	
Number entered	16
Number evaluable for toxicity	16
Men/women	12/4
Median age (range)	55 (21–76) years
Performance status (CALGB):	
0	9
1	4
2	3
Prior chemotherapy	16
Prior radiotherapy	6
Histologic subtype:	
Leiomyosarcoma	4
Malignant fibrous histiocytoma	3
Alveolar soft-parts sarcoma	2
Malignant schwanoma	2
Rhabdomyosarcoma	1
Liposarcoma	1
Chondrosarcoma	1
Extraosseous osteogenic sarcoma	1
Synovial-cell sarcoma	1
Sites of disease:	
Pulmonary	8
Liver	3
Retroperitoneum	1
Paravertebral	1
Locally unresectable primary	6
Median number of cycles of trimetrexate (range)	3 (1–12)
Toxicity (CALGB grade):	
Granulocytopenia (cells/μl):	
≥4000	3
3,000–3,900	1
2,000–2,900	3
1,000–1,900	5
<1,000	3
Thrombocytopenia (platelets μl)	
≥150,000	11
75,000–150,000	2
50,000–74,900	0
25,000–49,900	0
<25,000	3
Mucositis grade:	
0	12
1	0
2	4
Rash:	
None	13
Local erythema	2
Generalized erythema	1
Diarrhea grade:	
0	14
1	2
Renal toxicity:	
0	15
Creatinine >1.5 × normal (2.5 mg/dl)	1

by 2 mg/m^2 per day if grade 3 or 4 toxicity was observed. Complete blood counts were obtained weekly while patients were under study.

Results

A total of 16 patients were entered and treated with trimetrexate; all were evaluable for toxicity and 15 were evaluable for response (Table 1). The unevaluable patient developed diffuse skin erythema, mucositis, and pancytopenia after one cycle of therapy and was not given a second course. After one cycle of therapy this subject exhibited stable disease. Toxicity (Table 1) was predominantly hematologic, with grade 3 or 4 granulocytopenia being noted in half of the patients and grade 4 thrombocytopenia developing in three subjects. In five cases the dose of trimetrexate was increased until grade 2 neutropenia was observed. One patient who had undergone a hemipelvectomy required a dose reduction after one treatment cycle due to pancytopenia. Despite dose escalation, no life-threatening hematologic toxicity was noted. A 76-year-old woman with a low albumin level of 3.3 mg/dl was treated at a reduced dose of 6 mg/m^2 trimetrexate daily but died 2 weeks after treatment, exhibiting rapidly progressive disease (new soft-tissue lesion and ascites) in addition to thrombocytopenia and azotemia, the latter perhaps being treatment-related. Mucositis (4/16) and skin rash (3/16) were also noted after trimetrexate treatment.

No partial or complete responses were noted. Six patients displayed stabilization of disease for intervals ranging from 2 to 9 months. The 95% confidence interval (exact binomial method [11]) of the true rate of response of soft-tissue sarcomas to trimetrexate was 0 to 22%.

Discussion

This negative study (0/15) is consistent with the low response rate noted in a Canadian study [9] in which 3 of 22 (14%) evaluable patients showed short partial responses. One responder had not received prior treatment for metastatic disease. Thus, in a patient population comparable with our own, 2 of 21 subjects responded partially (10%), within the confidence interval of the present trial. The pooled rate of response of soft-tissue sarcomas to high-dose methotrexate is 13% and that to intermediate-dose methotrexate is 21% [3]. Trimetrexate administration appears to result in a similar response rate.

The major toxicity was myelosuppression, with mucositis being less prominent. Many patients exhibited no toxic effects at the initial dose of 8 mg/m^2 daily and developed toxicity only following dose escalation. Despite this relationship of dose escalation with toxicity, we could not demonstrate a major antitumor effect. Trimetrexate, shows no evident activity at this dose and on this schedule in patients with soft-tissue sarcomas refractory to a doxorubucin-containing regimen. Trimetrexate should be tested in combination with effective agents such as doxorubicin or ifosfamide so as to define its efficacy prior to the development of drug resistance.

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