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Clinical report

Phase II study of raltitrexed ('Tomudex') for patients with advanced soft tissue sarcomas refractory to doxorubicin-containing regimens

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Advanced soft tissue sarcomas (ASTS) refractory to therapy with doxorubicin and/or ifosfamide are highly resistant to therapy with other cytotoxic agents.The efficacy and safety of raltitrexed ('Tomudex') was assessed in patients with ASTS refractory to one or two doxorubicin- and/or ifosfamide-containing regimens in eight centers of the EORTC STBSG group. Raltitrexed was given at 3 mg/m^2 as a 15 min i.v. infusion once every 3 weeks. Among the 23 patients [mean age 54 (range 25–73) years] included, 22 patients (15 males and seven females) were eligible and evaluable for response to therapy and 21 were evaluable for toxicity. Patients had previously received chemotherapy in metastatic phase ($n=16$), as adjuvant treatment ($n=5$) or both ($n=1$). The primary tumor was located in the trunk ($n=11$), in the limbs ($n=8$) or in the head and neck ($n=3$). Most patients ($n=13$) received two courses of raltitrexed (range 1–8).The best response was stable disease in five (23%) patients, while disease progression was noted in 17 patients (77%); the median time to disease progression was 6 weeks. The treatment was well tolerated with only one patient experiencing grade 4 neutropenia and thrombocytopenia, one patient experiencing grade 3 nausea, one lethargy, one headache, and one asthenia. Only one patient experienced febrile neutropenia. Raltitrexed as monotherapy is not an effective treatment for patients with ASTS who failed conventional chemotherapy with doxorubicin and ifosfamide. [© 1999 Lippincott Williams & Wilkins.]

Key words: Advanced soft tissue sarcoma, chemotherapy, doxorubicin, drug resistance, EORTC, ifosfamide, phase II trial, raltitrexed, sarcoma, Tomudex.

Introduction

Doxorubicin remains the most effective treatment in patients with advanced soft tissue sarcoma (ASTS).[1,2] Furthermore, those patients with tumors refractory to therapy with doxorubicin- and ifosfamide-containing regimens have limited treatment options.[3–7] Although high-dose ifosfamide, DTIC, etoposide and platinum compounds have all been reported to yield occasional responses in this setting, well-designed prospective clinical trials have shown that response rates with these agents are consistently less than 20% and that the duration of response is short.[6–14] Recently available drugs such as taxanes,[15–18] topotecan,[19] vinorelbine[20] and gemcitabine[21] have also been evaluated in chemotherapy-naive and refractory patients with ASTS but the results have been disappointing. It is therefore crucial to identify new drugs active in this disease.

Raltitrexed ('Tomudex') is a quinazoline folate analog which acts as a direct and specific inhibitor of thymidilate synthase.[22] This agent is effective against colorectal carcinoma and it is associated with response rates that are similar to those achieved with 5-fluorouracil and low-dose leucovorin in this setting.[23] Objective responses have also been reported in other tumor types including breast cancer, non-small cell lung cancer, ovarian cancer and pancreatic cancer.[24]

This phase II study was conducted to assess the efficacy and tolerability of raltitrexed in patients with ASTS refractory to standard doxorubicin- and/or ifosfamide-containing regimens.

Patients and methods

Inclusion and exclusion criteria

Patients aged over 15 years with histologically proven locally advanced and/or metastatic soft tissue sarcoma were eligible for inclusion. Patients were also required

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to have progressive and measurable disease, an ECOG performance status of 0–1, a life expectancy of at least 3 weeks and laboratory values within defined limits (granulocyte count > 1500 cells/μl, platelet count > 100 000 cells/μl, bilirubin < 20 μM/l, serum creatinine < 120 μM/l or creatinine clearance > 60 ml/min). All histological slides were externally reviewed, according to the standard procedure of the EORTC STBSG group. No concurrent therapy was allowed and patients were required to give written informed consent prior to inclusion. The study received approval from the local ethics committee and was conducted in agreement with the principles of the Declaration of Helsinki.

Treatment

Patients received raltitrexed 3 mg/m^2 as a 15 min i.v. infusion every 3 weeks. Dose adaptations were made in the second and subsequent courses of treatment if severe hematological and non-hematological toxic effects were observed and resolved. Patients received 75% of the preceding dose if they experienced grade III or IV haematological toxicity and 50% of the preceding dose if they experienced grade III non-haematological toxicity. For any patient who experienced grade IV non-hematological toxicity, treatment was stopped.

The dose amendments were continued for all subsequent courses, unless further dose reduction was necessary. Doses were never re-escalated. Patients who develop grade III or IV toxicity after dose reduction stopped trial therapy. In the event of toxicity, dose administration was delayed for a maximum of 21 days, until all signs of toxicity were resolved. If after a delay of 21 days there was no improvement, the patient was withdrawn. Patients with a creatinine clearance of 25–65 ml/min received 50% of the planned dose (i.e. 1.5 mg/m^2) once every 4 weeks.

Response criteria

Response to therapy was evaluated every 6 weeks (after every second cycle). Complete response (CR) was defined as a complete disappearance of all known disease, determined by two observations not less than 4 weeks apart. Partial response (PR) was defined as a 50% or greater decrease in total tumor size (relative to the baseline measurement), determined by two observations not less than 4 weeks apart, with no appearance of new lesions or progression of any lesion. Progressive disease (PD) was defined as a 25% or greater increase in the size of one or more measurable lesions (relative to the smallest tumour size measured since treatment start), or the appearance of new lesion(s). No change (NC) was recorded when neither a complete nor a partial response nor a progression had been demonstrated at least 6 weeks after the start of treatment. When a CR was recorded for the target lesion(s), a PR or NC in a non-target lesion was recorded as a PR. The evidence of progression of any lesion or appearance of a new lesion was recorded as PD. All objective responses had to be reviewed and confirmed by external experts.

Table 1. Patient characteristics

	Median (range)	*N* (%)
Age	54 (25–73)	
Sex		
female		7 (32)
male		15 (68)
Performance status		
0		10 (45)
1		12 (55)
Histology		
leiomyosarcoma		8 (36)
angiosarcoma		3 (14)
synovialosarcoma		2 (9)
liposarcoma		2 (9)
malignant fibrous histiocytoma		1 (4.5)
neurosarcoma		1 (4.5)
alveolar rhabdomyosarcoma		1 (4.5)
unclassified sarcoma		2 (9)
others		2 (9)
Primary tumor sites		
visceral (intra-abdominal)		6 (27)
knee		5 (23)
thigh		3 (14)
retroperitoneal		2 (9)
other front trunk		2 (9)
uterus		1 (4.5)
neck		1 (4.5)
scalp		1 (4.5)
face		1 (4.5)
Previous surgery		
yes		18 (82)
no		4 (18)
Previous radiotherapy		
yes		12 (55)
no		10 (45)
Previous chemotherapy		
in adjuvant phase		5 (23)
in metastatic phase		16 (73)
both		1 (4.5)

Statistical considerations

The principal objective of the trial was to assess the therapeutic activity of raltitrexed in patients with ASTS by determining the CR and PR variables and the duration of response.

The trial was conducted in two stages, using the Minimax design.[25] The trial was conducted on the basis of the assumption that a response rate of 10% or less would indicate that further investigation of the drug was not warranted and that a response rate of 30% or greater would warrant further investigation. The accepted probability (α) of recommending a further trial with a true response rate 10% or less was taken as 0.05. The accepted probability (β) of rejecting a further trial when the true response rate was 30% or greater was taken as 0.1. Using these assumptions 33 patients were required. The trial would, however, be discontinued early if two or less responses were observed in the first 22 evaluable patients recruited. If this criterion was not met accrual was to continue until 33 patients were evaluable for response. If six or less responses were observed in this population, the trial was stopped with the conclusion that the drug should not be further investigated further. If more than responses were to be observed, the trial was stopped and further investigations recommended.

Results

Description of the patients

Twenty-three patients with histologically proven locally advanced and/or metastatic soft tissue sarcoma with progressive disease were enrolled: 21 were evaluable for toxicity and 22 for response. The clinical and biological characteristics of these patients and their tumors are depicted in Table 1. The median age was 54 years (range 25-73). There were 15 (68%) males and seven (32%) females, with an ECOG performance status of 0 for 10 (45%) patients and 1 for 12 (55%) patients. Leiomyosarcoma ($n=8$, 36%) was the predominant histological diagnosis (Table 1). All patients received previous chemotherapy, as adjuvant therapy ($n=5$) in metastatic phase ($n=16$) or both ($n=1$). A total of 52 raltitrexed courses was given (median 2; range 1-8). Three (14%) patients completed six courses of treatment and 19 progressed before completion of six cycles.

Table 2. Toxicity of the treatment

	Number of patients (%) at grade					
	0	1	2	3	4	Not related
Hematological toxicity (WHO grade)						
leukocytes	17 (81)	3 (14)	0	1 (5)	0	-
neutrophils	16 (76)	2 (9)	2 (9)	0	1 (5)	-
platelets	20 (95)	0	0	0	1 (5)	-
hemoglobin	11 (52)	6 (29)	4 (19)	0	0	-
Non-hematological toxicity (NCIC grade)						
allergy	20 (95)	1 (5)	0	0	0	0
fever	16 (76)	1 (5)	4 (19)	0	0	3 (14)
febrile neutropenia	20 (95)	0	0	1 (5)	0	0
arthralgia	20 (95)	0	1 (5)	0	0	1 (5)
lethargy	12 (57)	6 (28)	2 (9)	1 (5)	0	3 (14)
myalgia	20 (95)	0	1 (5)	0	0	2 (9)
other flu-like	20 (95)	0	1 (5)	0	0	0
anorexia	19 (95)	1 (5)	1 (5)	0	0	1 (5)
diarrhea	15 (72)	3 (14)	3 (14)	0	0	2 (9)
nausea	12 (57)	6 (28)	2 (9)	1 (5)	0	1 (5)
vomiting	17 (81)	1 (5)	3 (14)	0	0	0
pain/cramping	20 (95)	0	1 (5)	0	0	1 (5)
stomatitis	18 (85)	2 (9)	1 (5)	0	0	0
headache	19 (90)	1 (5)	0	1 (5)	0	1 (5)
alopecia	20 (95)	1 (5)	0	0	0	5 (24)
skin rash	19 (90)	2 (10)	0	0	0	0
weight loss	19 (90)	2 (10)	0	0	0	1 (5)
asthenia	18 (85)	2 (9)	1 (5)	0	0	2 (9)

Response

No objective CR or PR and no minor responses were seen. Seventeen (77%) patients had PD at first evaluation and five (23%) patients experienced no change as a best response. The median time to progression was 6 weeks. At study end, seven of the 22 patients had died, all due to tumor progression.

Toxicity

Raltitrexed was generally well tolerated (Table 2). Only one patient experienced grade 4 neutropenia and thrombocytopenia, and another febrile neutropenia. One patient experienced grade 3 nausea, one experienced grade 3 lethargy, one grade 3 headache and one grade 3 asthenia.

Discussion

Advanced non-resectable soft tissue sarcomas are poorly susceptible to cytotoxic chemotherapy. Indeed, doxorubicin and ifosfamide are the only drugs that are effective as single-agent therapy in this disease. Although combination chemotherapy regimens may increase response rates compared to single-agent regimens in these patients, they have not increased survival in well-designed prospective clinical trials.[2,26,27]

The activity of other drugs has remained disappointedly low when used as first-line monotherapy in patients with ASTS. Typically, response rates fall below 20%, e.g. 18% for DTIC,[8,9] 15% for cisplatin,[12] 12% for carboplatin,[13] 0–11% for taxotere,[15–17] 12.5% for paclitaxel and 13% for topotecan.[19]

Not surprisingly, response rates are no better in patients with ASTS who have not responded to previous chemotherapy with doxorubicin and/or ifosfamide. Although response rates of 30% or greater have been reported for high-dose ifosfamide (12– 15 g/m^2) in single-center studies of patients who have progressed following treatment with doxorubicin-containing regimens,[5,6] only 15% of patients responded to this regimen in a recent well-designed multicentric prospective study.[7] Navelbine and gemcitabine were recently reported to yield respective response rates of 11 and 20% in this setting but the number of patients recruited to each study was very low.[20,21]

In the present trial, raltitrexed was not effective in patients with ASTS refractory to doxorubicin- and/or ifosfamide-containing regimens. Only 23% of the patients achieved stable disease and there were no objective responses in this difficult-to-treat population. Raltitrexed was, however, generally well tolerated. Given the refractory nature of doxorubicin-resistant ASTS, further studies with new agents that have novel mechanisms of action (e.g. angiogenesis and metalloprotease inhibition) are clearly warranted.

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