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Phase II Study of Elliptinium in Metastatic Soft Tissue Sarcoma

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Abstract—*A phase II study was carried out with 9-hydroxy-methyl-elliptinium (9-HME) in metastatic soft tissue sarcoma. The dose was* 100 mg/m² *weekly in* 1½ hr *intravenous infusion protected from light. Nineteen cases were evaluable for response, all previously treated with other chemotherapy regimens. No remissions were seen. Major toxicities were nausea and vomiting, dryness of the mouth and anorexia. It is concluded that 9-HME is not an effective drug in metastatic soft tissue sarcoma.*

INTRODUCTION

THE NUMBER of drugs useful in soft tissue sarcoma is very limited. In the EORTC Soft Tissue and Bone Sarcoma Group a number of phase II studies in metastatic soft tissue sarcoma have resulted in negative conclusions (cisplatin, methotrexate, carminomycin, etoposide). Elliptinium and its derivatives are plant alkaloids which exhibit tumor activity probably by DNA intercalation. 9-Hydroxy-2-*N*-methyl elliptinium (9-HME) showed a favorable therapeutic index in L1210 leukemia [1, 2].

A phase II study with this new compound was designed in patients with locally recurrent and/or metastatic soft tissue sarcomas to determine the activity of the drug.

On the basis of prior phase I and II studies [2–5] a dose of 100 mg/m² weekly was chosen. At this dose side-effects were anorexia, nausea and mouth dryness; hematologic toxicity was minimal. Severe hemolysis due to antibody formation was observed [6].

MATERIALS AND METHODS

Patients included in the study had histologically proven soft tissue sarcoma with progressive locally recurrent or metastatic disease (Table 1). The age of the patients was between 28 and 70 yr. All had normal liver and kidney function and had not been treated in the previous

Table 1. Characteristics of 19 patients

Sex	
Male	8
Female	11
Age (yr)	
Median	46
Range	28–70
Previous radiotherapy	
Yes	8
No	11
Previous chemotherapy	
One drug	2
Several drugs	17
Site of disease	
Locoregional	4
Distant metastases	11
Both	4
No. of courses	
Median	4
Range	2–9
Histopathology of tumors	
MFH	3
Liposarcoma	3
Leiomyosarcoma	3
Fibrosarcoma	2
Synoviosarcoma	2
Epitheloid sarcoma	2
Unclassified	2
Angiosarcoma	1
Neurofibrosarcoma	1

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4 weeks. The drug was administered at a dose of 100 mg/m² weekly in 1½ hr intravenous infusion in 500 ml 5% dextrose, protected from light. The dose was reduced to 75% if leucocytes were between 2 and 3×10^9/l or the platelets between 75 and 125×10^9/l. Below these values treatment was delayed for one week. In case of unexpected side-effects such as hypotension or hemolysis, treatment was stopped.

Antibodies to 9-HME were determined, and if the titer rose above 1:8 treatment was also stopped [6].

Evaluation of remission status was done according to the standard phase II protocol of the Group.

After four doses of the drug a first evaluation was done; in case of progression treatment was stopped, otherwise treatment continued to at least eight courses before a second evaluation.

RESULTS

Twenty-six patients were entered into the study, four of whom were not eligible because of pathology: one carcinoma, one mesothelioma, one osteosarcoma and low Karnofsky index (one patient). Three other patients could not be evaluated: in one patient treatment was never started, in two there were insufficient data to evaluate toxicity or response. Nineteen patients were fully evaluable. The clinical data are given in Table 1.

The median number of doses given was four, with a range of 2-9 courses. In these courses a median of 97% of the prescribed doses was administered (range 59-102%).

At first evaluation after four doses there was progressive disease in 10/19 cases, and eight were evaluated as no change. One patient refused treatment after two courses because of fever and complaints of a dry mouth. In eight patients treatment was scheduled to continue. In one of them, however, treatment was changed to MTX and in one other it was stopped due to toxicity after the fourth course. Two patients received six injections; in one it was stopped because of anorexia and dryness of the mouth and in the other progression occurred simultaneously with development of 9-HME antibodies. Two patients were given seven injections and treatment was stopped because of progression in one and development of antibodies 1 month later followed by progression in the other. The two other patients received eight and nine courses respectively; disease progressed 3 and 6 weeks after the end of treatment. No complete or partial remissions were observed.

Nausea and vomiting occurred in all patients. In 18 it was WHO grade 1 or 2, in only one was it grade 3.

Mouth dryness occurred in 15 patients, in five being scored as grade 3 with stomatitis and ulceration, requiring liquid diets. In three patients it was severe enough to stop treatment. Anorexia occurred in 14 patients, thrombophlebitis in eight. Side-effects occurring less frequently were fever (six cases), drowsiness (three cases) and constipation (two cases). Two patients developed 9-HME antibodies after six and seven injections respectively leading to cessation of the drug. Hematologic toxicity, hypotension, hemolysis or nephrotoxicity were not observed.

DISCUSSION

From the data presented it can be concluded that 9-HME is not an effective drug in the treatment of soft tissue sarcoma. There were no objective remissions in the 19 patients studied. In patients with initially no change, disease progressed rapidly during or shortly after the treatment. The first courses of the drug were well tolerated, but during further treatment mouth dryness, ulceration and anorexia were unpleasant side-effects. Although occasional, severe hemolysis has been observed in other studies. This was not the case in our group of patients. The development of antibodies in the serum prevented further treatment in two patients who might have developed hemolysis after subsequent injections.

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