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Phase II study of 5'-deoxy-5-fluorouridine (doxifluridine) in advanced malignant melanoma

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Summary. Forty-two patients with malignant melanoma were treated with doxifluridine, 4000 mg/m^2 daily $\times 5$, repeated every 3 weeks. The daily dose was reduced to 3000 mg/m^2 in patients who had experienced severe myelosuppression with prior chemotherapy. A total of 35 patients were evaluable for response, and 25 of these received two or more courses. Two responses were observed. Toxicity mainly took the form of nausea, vomiting, stomatitis, dizziness, ataxia, and fatigue. Mild leukopenia was frequent (43%). Nadir counts $< 1.5 \times 10^9$/l leukocytes or 50×10^9/l platelets were seen in 7% and 2% of the courses respectively. Doxifluridine has no useful activity against malignant melanoma.

Introduction

Malignant melanoma is a tumor frequently selected for disease-oriented phase II trials, because of its poor responsiveness to available chemotherapy. Doxifluridine (5'-dFUrd) is a fluorinated pyrimidine with reduced myelosuppressive and experimental efficacy against 1210 leukemia, Crocker sarcoma S 180, B-16 melanoma, and Lewis lung carcinoma [6]. Clinical studies have found tumor responses in carcinomas of the colon and rectum, stomach, head and neck, breast, lung, and endometrium [1–3, 7].

Doxifluridine is a prodrug releasing fluorouracil (5-FUra) within the cell through the action of uridine phosphorylase [4, 8, 10], an enzyme previously demonstrated to have high activity in 5'-dFUrd-sensitive tumors and low activity in the bone marrow [5]. Leyva et al. have measured the uridine phosphorylase activity in various human tumor samples and found the highest value in malignant melanoma [9]. It was speculated that tumors with high activity of uridine phosphorylase might be responsive to 5'-dFUrd even if apparently resistant to 5-FUra. On this basis the EORTC Early Clinical Trials Group investigated the antitumor effect of doxifluridine and its tolerance in patients with advanced malignant melanoma.

Materials and methods

Patients with measurable or evaluable lesions of recurrent or metastatic histologically confirmed malignant melanoma were eligible. Other requirements include blood counts, serum bilirubin and creatinine levels within normal values, and absence of radiotherapy or chemotherapy during the last 4 weeks before treatment. In all, 42 patients (25 male and 17 female) with a median age of 50 years were treated, 39 of whom had cutaneous melanoma and 3, extracutaneous primary lesions (1 in the tonsil, 1 in the ovary, and 1 in the choroid). Six patients had had prior radiotherapy and 24 prior chemotherapy. The performance status (ECOG scale) was 0–1 in 34 patients and 2 in all others. Seven patients were excluded from the analysis of response. Two did not fulfill the eligibility criteria, one received an inadequate drug dose, one had a leg amputation shortly after initiation of treatment, and for three the study documentation was incomplete.

Doxifluridine was given by IV injection on days 1–5 and repeated every 3 weeks or more, depending upon the intensity and duration of toxicity. Patients who had experienced severe myelosuppression with prior chemotherapy were started at a daily dose of 3000 mg/m^2 and all other patients, at 4000 mg/m^2. Whenever possible, patients received two treatment cycles before response evaluation.

Results

Thirty-five patients were fully evaluable for tumor response. Ten patients received only one cycle of treatment, nine because of rapidly progressive disease and one because of death from tumor progression within 3 weeks of the initiation of therapy. Twenty-five of the patients evaluable for response received two or more courses of therapy. Toxicity was evaluated independently of responses. Eighty-two treatment cycles in thirty-four patients were evalu-

Table 1. Characteristics of doxifluridine treatments

	Treatment cycles					
	1	2	3	4	5	6
No. of evaluable treatments	34	23	13	7	4	1
No. of treatments with						
$\geq$90% of 4000 mg/m^2/day * $\times 5$	24	20	7	6	2	1
$\geq$90% of 3000 mg/m^2/day * $\times 5$	9	1	1	0	0	0
<90% of theoretical dose	1	2	5	1	2	0
Delay of 1–4 weeks		2	3	6	4	0
Mean percentage of theoretical dose	98	95	88	89	80	100

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Table 2. Toxicity

	Treatment cycles 1	2	3–6	Percentage of treatments with toxicity
Total no. of cycles	34	23	25	
No. of cycles with				
Nadir leukocytes				
$<3.5 \times 10^9$/L	15	8	12	43
$<1.5 \times 10^9$/L	4	2	0	7
Nadir thrombocytes				
$<150 \times 10^9$/L	6	2	3	13
$< 50 \times 10^9$/L	1	1	0	2
Nausea, vomiting	18	9	7	41
Neurological	4	5	5	17
Stomatitis	5	3	3	13
Skin	3	4	3	12
Diarrhea	4	2	0	7
Drug fever	1	0	2	4
Hair loss	0	1	1	2
Cardiac	0	1	0	1

able for toxicity. Table 1 summarizes the evaluable treatments with the percentage of the theoretical dose and the number of treatments with a delay of 1–4 weeks.

One complete and one partial response were observed. Both patients had been previously treated with vindesine + cisplatin and vindesin + cisplatin + DIC. Their measurable lesions were metastatic lymph nodes. The response durations calculated from day 1 of treatment to tumor relapse were 224 and 50 days. Five patients had stable disease for 71–155 days. The tumor was progressive in all other patients.

Table 2 summarizes the drug-related toxicity. Significant leukopenia or thrombopenia was observed in only 7% and 2%, respectively, of the treatment courses. Myelosuppression was not cumulative. Leukopenia was the main reason for dose reduction or treatment delay. Nonhematologic toxic effects were always mild and reversible. Neurologic manifestations were observed in 17% of courses. These consisted mainly in dizziness, ataxia, and fatigue. A few patients also complained of peripheral dysesthesia. Cutaneous toxicity included one case of skin rash, whereas for all other treatments it consisted in the previously described sensation of localized or generalized "hot flushes" on the skin. Hair loss was always partial. Reversible sinus tachycardia was observed after the second treatment course in one patient.

Discussion

The doxifluridine dose used in this trial was defined in a previous phase I study [1], and was identical with that used in other phase II studies [2, 3]. In this series drug tolerance was remarkable, suggesting that higher dosages would have been possible, with a potentially higher response rate. However, previous phase I experience showed that the dose could not be increased above 4000 mg/m^2 without unbearable toxicity. The tolerance of 5-dFUrd seems to be related to the patients' general condition at least with a daily $\times 5$ schedule. A large majority of our patients had a favorable performance status. In another series of advanced head and neck cancer patients, whose general condition was poor, the same dose schedule produced significantly higher toxicity [3].

Two responses were observed in 35 evaluable patients. Even if only the 25 patients with two or more treatment cycles are considered in the definition of the response rate our conclusion is that doxifluridine has no useful activity in the treatment of malignant melanoma.

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