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Phase II Study of Estramustine Phosphate (Estracyt®) in Patients with Metastatic Melanoma

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Abstract—*Twenty-six patients with measurable metastatic melanoma were treated with estramustine phosphate* (12 mg/mg *body wt*) *orally every day. Tumor biopsies were assessed for estrogen receptors* (*ER*) *in* 14 *patients and for estramustine binding sites* (*EMBS*) *in* 13 *patients. ER and EMBS were measured with isoelectric focusing in polyacrylamide gels. Three partial responses* (*PR*) (12%) *and three no changes* (*NC*) (12%) *according to WHO criteria were registered. In one patient with NC and in four patients with progressive disease* (*PD*) *the tumors were ER positive. EMBS was found in one patient with PR and in two patients with PD. Because of the low frequency of antitumor activity and the low number of patients with ER and/or EMBS the number of patients is too low for any correlation between tumor response and ER and/or EMBS status.*

INTRODUCTION

THERE are few cytostatic agents proved to be effective in the treatment of patients with metastatic melanoma. The most established single agent is Dacarbazin® (DTIC) with response figures of 16–24% using various dose schedules. DTIC in combination with other agents has not increased these figures significantly but produced considerably more toxicity. With this background and the thought that melanoma might to some extent be a hormone-dependent tumor, we decided to further explore the effect of estramustine phosphate (Estracyt®). Estramustine phosphate is a nor-nitrogen mustard derivate bound to estradiol-17β-phosphate which has been used since 1966 in the treatment of prostatic cancer. There is one phase II study of estramustine phosphate in metastatic melanoma [1].

The presence of estrogen receptors (ER) in melanoma tumor biopsies has been reported [2–5]. In our laboratory ER was detected at low concentrations (0.2–14 fmol/mg protein) in 70% of the samples from melanoma metastases [6]. There are other investigators who have failed to demonstrate any measurable amount of ER and there is doubt that ER actually are found in melanoma tissue [7–10]. Recently a binding site for estramustine (EMBS) was found [11]. Estramustine and estromustine are the cytotoxic metabolite of estramustine phosphate. In 95 different samples of melanoma metastases from 77 patients EMBS was detected in 15 patients (20%) [11].

The rationale behind the present study was to further evaluate estramustine phosphate in advanced melanoma, especially when given as first line chemotherapy, and if possible correlate the tumor remission with EMBS and ER.

Table 1. *Characteristics of evaluable patients*

Number of patients	26	
Male/female	18/8	
Median age (range) years	54	(22–79)
Prior therapy		
None	25	
Chemotherapy	1	
Dominant site of metastases		
Subcutaneous	7	
Lymph nodes	2	
Lung	12	
Liver	3	
Other viscera	1	
Bone	1	
Multiple metastatic sites	8	

MATERIALS AND METHODS

Twenty-seven patients with metastatic melanoma were included in the study from January 1985 to August 1986 (Table 1). All patients had a

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Table 2. The distribution of tumor response in relation to the occurrence of estrogen receptors (ER) and estramustine binding sites (EMBS)

	ER			EMBS		
	+	−	No analysis	+	−	No analysis
Partial response	0	2	1	1	1	1
No change	1	0	2	0	1	2
Progressive disease	3	8	9	2	8	10

measurable disease and/or evaluable lesions according to WHO criteria and Karnofsky performance status was more than 60 [12]. All patients gave their informed consent. The pre-treatment evaluation included laboratory tests, chest radiography, liver scan and/or ultrasonography of the liver. Physical examination, laboratory tests and any other investigation necessary for the evaluation of the treatment were performed evey 6 weeks. Tumor response was evaluated according to WHO criteria [12]. The duration of partial response (PR) and no change (NC) was recorded from the first day of treatment to the day of first observation of progressive disease (PD). The treatment was discontinued when signs of PD or when the side-effects were not tolerated. Time to PD and the duration of response or NC was measured from the onset of treatment until progression was registered. The dose of estramustine phosphate (Estracyt®) was 12 mg/kg body wt/day and was given orally by tablets 140 mg each.

ER and EMBS were analysed by isoelectric focusing [13, 14]. The level of sensitivity for ER was 1.0 fmol/ml [13]. The ER concentration was expressed per unit protein (fmol ER/mg protein), which was determined according to Lowry *et al.* [15]. EMBS was only stated as positive or negative [14].

RESULTS

Twenty-six out of 27 patients were evaluable. One patient discontinued the treatment after 21 days because of intolerable nausea and vomiting. No patient had a complete response. Three patients achieved PR (12%), two of these patients had subcutaneous metastases and one lymph node metastases as the dominant site. The durations of response were 3, 4 and 17 months, respectively. No change was registered in three patients (12%) with lung metastases during 2, 3 and 16 months. The median duration and range to time of progression for evaluable patients were 2 months and 2–17 months.

Toxicity was mild to moderate nausea in eight patients, vomiting in three, mammary glands pain in five, weight gain in two and a lower extremity venous thrombosis in one. The dose was reduced in 2/8 patients with nausea.

ER was measured in 14 patients and EMBS was measured in 13 patients. Five of 14 patients had ER positive tumors (range 1.7–7.7 fmol/ER mg/protein) of whom one patient was classified as NC and four as PD. Three of 13 patients had EMBS positive tumors, one with PR and two with PD (Table 2).

DISCUSSION

In a previous phase II study of 26 patients with advanced malignant melanoma estramustine phosphate was given as third-line chemotherapy. Complete response was registered in one patient with subcutaneous disease, who remained in remission for 3 years and in three other patients NC was registered for a period of 3–5 months [1]. The authors suggested that a trial in patients with ER positive tumors had to be done. Recently one of those authors reported an adjuvant study of 82 patients with stage II melanoma treated with DTIC and estramustine phosphate without any significant difference compared to an untreated group of patients [16]. The number of patients was too small for any conclusion. Other studies using different endocrine regimens have shown limited tumor response and neither any correlation between tumor remission and the occurrence of ER [17].

A somewhat better result should be expected when estramustine phosphate was given as first-line therapy. The response in the present study with dominant tumor sites in subcutaneous tissue, lymph nodes and lungs was on the whole in accordance with Lopez *et al.* [1]; however, tumor remission was rather short. Analyses of ER and EMBS were not possible in more than half of the patients because some metastases were unaccessible. In a previous study with an analysis of 95 samples of melanoma in 77 patients the frequency of EMBS positivity was 20% [11]. This was also confirmed in this series of patients.

In conclusion estramustine phosphate can have some antitumor activity in melanoma preferentially in soft tissue and lung metastases. With a low response rate and a low frequence of EMBS positive samples it was not possible to draw conclusions of any correlation between tumor response and ER

and EMBS status. Although this study cannot answer the question it is still of interest to further investigate estramustine phosphate in patients with EMBS positive melanoma metastases.

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