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Phase II Study of 9-Hydroxy-2*N*-methylellipticinium Acetate*

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On behalf of the EORTC Early Clinical Trials Group

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Abstract—*A broad phase II trial of elliptinium was conducted in 105 evaluable patients with advanced solid tumors. The drug was given as a 60–90-min i.v. infusion at a weekly dose of 100 mg/m². Of 36 breast cancer patients, one achieved complete and six achieved partial response for an overall response rate of 19%. Responses lasted for 12–56 weeks from initiation of therapy. There was also one partial response among 21 patients with squamous cell carcinoma of the lung. No response could be obtained in 17 patients with colon cancer, 13 patients with head and neck cancer and 18 patients with a wide variety of other malignancies. Myelosuppression was minimal. Nausea and vomiting were the most frequent toxic effects. The drug also produced serious xerostomia and acute intravascular hemolysis. Asthenia was common. Other adverse reactions included fever and chills, transient neurologic and cardiovascular manifestations and renal function impairment. Additional work is needed to define optimal modes of drug administration.*

INTRODUCTION

9-HYDROXY-2*N*-METHYLELLIPTICINIUM acetate (elliptinium) is a new anticancer ellipticine derivative [1]. A phase I study with weekly doses of 80–160 mg/m² identified neurologic manifestations as dose-limiting [2]. Acute reactions, such as profound hypotension, tachycardia and dyspnea, occurred with rapid i.v. injection. Following single doses of 15–80 mg/m² daily for 5 consecutive days, the drug produced dose-related and dose-limiting asialia as well as frequently severe local phlebitis [3]. With either schedule nausea and vomiting were commonly encountered, whereas myelosuppression was minimal.

Pharmacokinetic investigations in patients with normal hepatic and renal functions showed wide variations in the plasma clearance of the drug [4]. Terminal half-lives between 8 and 51 hr were observed following 44–100-min i.v. infusions at doses of 80–95 mg/m². The corresponding urinary recovery accounted for 11–23% of the administered dose, suggesting that drug elimination was mostly extrarenal.

Between June 1978 and October 1979, the Early Clinical Trials Group of the EORTC conducted a broad phase II trial of i.v. weekly elliptinium. Preliminary data have already been reported elsewhere [5]. This paper summarizes the final analysis of the trial.

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MATERIALS AND METHODS

Patient selection

All eligible patients had pathologically proven solid malignancies. Eligibility criteria also included advanced disease with measurable or evaluable lesions, a Karnofsky score of at least 50, white blood cell count (WBC) $\geqslant 3000/\mu l$, platelet count $\geqslant 150{,}000/\mu l$ and adequate serum bilirubin and creatinine levels. No anticancer treatments were given for 3 weeks prior to entry. Patients with active infection, severe malnutrition and expected follow-up difficulties were excluded. Informed consent was obtained according to legal and institutional regulations in each participating center.

Treatment

The drug was supplied by the Centre de Recherches et d'Etudes Pharmacologiques, Chimiques et Médicales du Groupe Labaz, Paris, France, in vials containing a red-brown powder with 50 mg of elliptinium acetate. The compound was reconstituted with sterile water for injection and further diluted in 150–200 ml of dextrose 5% in water. The final solution was protected from light and administered i.v. over 60–90 min. The dose schedule of 100 mg/m^2 weekly was based on findings in a phase I trial undertaken within the framework of the new drug program of the EORTC Early Clinical Trials Group [2].

Response criteria

Complete response was defined as the disappearance of all symptoms and signs of the disease; *partial response* was a tumor shrinkage by 50% or more as measured by the product of the two largest tumor diameters. For lesions that did not lend themselves to accurate measurements, a reduction by at least 75% of the estimated volume was necessary; *no change* indicated tumor shrinkage that was insufficient to qualify for partial response or no increase in size of existing lesions; and *progression* consisted of the appearance of new lesions or an increase in the size of existing lesions, regardless of the response in other tumor areas.

Response duration was measured from initiation of therapy. Administration of at least three weekly doses of elliptinium was a prerequisite for an adequate trial.

RESULTS

A total of 130 eligible patients were entered by 15 institutions, of which two contributed 50% of the accrual. Twenty-two patients received less than three weekly doses because of progressive disease or rapid decrease in performance status (13 patients), treatment refusal (3 patients), toxicity (2 patients), early death (2 patients), intercurrent complication (1 patient) and loss to follow-up (1 patient). Response could not be evaluated in three additional patients: there was a major protocol violation in two and the indicator lesion became no longer assessable in one.

Of 105 evaluable patients, 36 had breast cancer, 21 had squamous cell lung cancer, 17 had colon cancer, 13 had head and neck cancer and 18 had a wide variety of other diagnoses (Table 1). The vast majority of breast cancer patients had been extensively pretreated; 60% of the remaining patients had prior chemotherapy (Table 1). Twenty-two patients received three weekly courses, 17 received four courses, 18 received five courses, 21 received six courses and 27 received more than six courses.

Among 36 women with breast cancer, 1 achieved complete response for 56 weeks and 6 had partial response for a median of 21 weeks, with a range of 12–32 weeks (Table 2). All responders had indicator lesions in the soft tissues, the skeleton or both. One had received no prior chemotherapy and six had been previously treated with combination chemotherapy regimens that included doxorubicin in two.

Table 1. Patient characteristics

Tumor type	No. of evaluable patients	Men/ women	Median age (range)	Median Karnofsky score (range)	Prior therapy RT	CT	RT + CT	Median No. of courses (range)
Breast	36	0/36	55 (19–77)	70 (50–100)	1	5	30	6 (3–48)
Lung (squamous)	21	19/2	62 (45–77)	80 (50–100)	2	4	4	4 (3–17)
Colon	17	7/10	58 (18–74)	70 (50–100)	3	9	0	5 (3–9)
Head and neck	13	12/1	58 (36–72)	70 (50–100)	2	2	9	6 (3–6)
Others*	18	10/8	50 (20–74)	70 (50–100)	1	8	6	4 (3–7)

*Lung (3 small cell and 3 adenocarcinomas), thyroid, kidney, soft tissue sarcoma (2 patients each), ovary, urothelial, stomach, gall bladder, penis and unknown primary (1 patient each).

Table 2. Response data

Tumor type	Total evaluable	No. of patients CR	PR	NC	PD
Breast	36	1	6	10	19
Lung (squamous)	21		1	10	10
Colon	17			3	14
Head and neck	13			2	11
Others	18			6	12

Among the 21 patients with squamous cell carcinoma of the lung, there was 1 partial response for 29 weeks in a patient previously treated with chemotherapy. No antitumor activity could be detected in the other tumor types.

A total of 31 patients went off-study with stable disease, 12 after three or four courses, 7 after five courses and 12 after six or more courses. Treatment was discontinued in nearly one-half of these patients because of toxic effects.

Adverse reactions were analyzed in 105 patients evaluable for response plus two patients in whom toxicity prevented the administration of more than two doses. Based on weekly counts, myelosuppression was mostly negligible even after extensive prior therapy. Of 102 patients entered with WBC $\geqslant 4000/\mu l$, 17% had leukopenia mainly of grade I according to WHO criteria (Table 3). None of the patients had grade IV leukopenia. Similarly, the effect on the platelets was minimal.

Nausea and vomiting were the most frequent toxic effects but gastrointestinal distress was severe in only 18% of the patients (Table 4). More significant was the development of xerostomia, commonly associated with considerable weight loss, which often required treatment withdrawal. Several patients complained of pronounced asthenia, but it was not always possible to establish whether this was drug-related. Local phlebitis was generally mild, although it resulted in treatment discontinuation in one patient.

Most disturbing was the occurrence of acute manifestations during drug infusion or immediately thereafter. These manifestations consisted of variable associations of fever, chills, drowsiness, dizziness, tremor, hypotension, chest pain, dyspnea, malaise restlessness and tachycardia. When drug infusion was withheld, rapid and spontaneous recovery was common. Improved tolerance was frequently noted when the treatment was resumed with slower drug administration for up to 3 hr. Occasionally, these signs and symptoms were accompanied by acute intravascular hemolysis. This phenomenon was demonstrated in six patients, of whom one developed oliguric renal failure requiring dialysis [6].

Table 4. Non-hematological toxic effects

Toxic effect	No. of toxic patients ($n = 107$)	
Nausea/vomiting	62	(18)*
Xerostomia	44	(14)
Fatigue	13	(4)
Phlebitis	13	(1)
Fever/chills	12	
Neurologic	10	(3)
Stomatitis	9	(3)
Diarrhea	9	
Renal	8	(1)
Alopecia	7	(1)
Hemolysis	6	(1)
Hypotension	5	(2)
Chest pain/dyspnea	3	
Malaise/restlessness	2	(2)
Tachycardia	2	

Numbers in parentheses represent the number of patients with WHO grade III–IV toxicity.

Serum creatinine elevations of 1.6–4.6 mg/dl were ascribed to elliptinium in eight other patients. In one of these, renal biopsy revealed interstitial nephritis. In addition, one patient with kidney tumor involvement died from renal failure, possibly triggered by drug administration.

Other toxic effects included stomatitis, diarrhea and alopecia. These effects were unfrequent and mostly mild to moderate.

DISCUSSION

The response rate in advanced breast cancer was promising, as also reported by others [7, 8]. In contrast, there was only one response in squamous cell lung cancer and none in the other malignancies. The number of patients with squamous cell lung cancer, colon carcinoma or head and neck cancer was adequate for statistically valid inferences. It is thus unlikely that elliptinium would prove active in any of these

Table 3. Myelosuppression

	Total patients	Toxic patients	No. of patients with WHO grade of toxicity I	II	III
WBC	102	17	11	3	3
Platelets	104	7	4	2	1

malignancies, although definite conclusions are not possible. The patient population was not favorable in terms of performance status and/or prior chemotherapy. Moreover, toxic effects often resulted in early drug discontinuation without any evidence of disease progression.

Elliptinium produces little or no myelosuppression, which would favor its incorporation into combination chemotherapy regimens. Yet, the drug is difficult to handle and may elicit significant toxicity in a substantial percentage of patients. Specifically, dryness of the mouth and acute intravascular hemolysis may seriously hamper elliptinium treatments.

Dryness of the mouth was reported in nearly one-half of our patients and was severe in one-third of these. Hypo- or asialia is slowly reversible. Resulting nutritional problems coupled with drug-induced asthenia may be very debilitating, especially in patients with far-advanced disease. The mechanism of xerostomia has not yet been elucidated. Of interest, distribution studies in mice have shown that the drug concentrates in the salivary glands [9]. A schedule-dependency of xerostomia is possible. In this respect, an intermittent schedule might be better tolerated than fractionated daily doses [3].

Hemolysis is probably related to drug-induced antibodies of the IGM type and is complement-mediated [6]. It is therefore suggested that the blood be tested for elliptinium-dependent antibodies before each drug administration [6, 10]. These antibodies agglutinate normal red cells only in the presence of drug and cross-react with some ellipticine derivatives but not with others. Of note, a direct hemolytic effect was reported with ellipticine, the parent compound [11].

Acute cardiovascular manifestations are occasionally dramatic but may be prevented to some extent. These reactions are transient and, generally, do not recur with slower infusions. Apparently, they are also less likely to occur with fractionated daily doses than with weekly administrations [3].

It would appear that elliptinium may also induce kidney damage. In our trial the relationship between drug administration and serum creatinine elevations could not be always ascertained. The type of damage and its kinetics need further documentation and preventative measures should be studied.

In conclusion, elliptinium is a new ellipticine derivative with anticancer properties in humans. Its spectrum of activity remains to be determined. The drug is poorly tolerated in a number of patients and it should be used with the greatest care. Additional work is needed to define effective methods for alleviating or circumventing serious adverse reactions and to establish how drug administration should be best monitored.

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