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Phase I Clinical Study of 9-Hydroxy-2*N*-methyl-ellipticinium Acetate (NSC-264137) Administered on a 5-Day i.v. Schedule*

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Abstract—*Twenty-three patients with advanced solid tumors received 9-hydroxy-2N-methyl-ellipticinium acetate at a single daily i.v. dose of* 15–80 mg/m^2 *for* 5 *consecutive* days, *repeated every* 3 weeks. *One partial and one minor response were achieved in two patients with breast cancer. Dryness of the mouth was dose-related and dose-limiting. Local phlebitis was also dose-related and frequently severe at the highest dose levels. Other non-hematologic toxic effects were essentially mild to moderate and included nausea, vomiting, diarrhea, stomatitis, fever, weakness, transient renal and hepatic impairment, alopecia and chest pain. Minimal myelosuppression was encountered. It appears that* 60 mg/m^2/day *is the maximum tolerated dose with a five-day schedule. According to our findings, this schedule does not seem to offer any advantage over the previously tested weekly administrations.*

INTRODUCTION

9-HYDROXY-2*N*-METHYL-ELLIPTICINIUM ACETATE (NSC-264137, HME) is a synthetic ellipticine derivative (Fig. 1) [1]. The drug has shown encouraging antitumor activity in advanced breast cancer [2–4]. As yet, HME has been essentially investigated at a weekly schedule and, with this mode of drug administration, neurologic manifestations consisting of weakness, apathy, intention tremor and memory loss have been reported to be dose-limiting [2]. These manifestations appear to be cumulative and more frequent in older patients. In a large-scale broad phase II trial [3], weekly administrations of 100 mg/m^2 produced nausea and vomiting (44%), dryness of the mouth (34%), stomatitis (23%) and neurologic toxicity (7%). Minimal myelosuppression was also encountered. In addition, this weekly regimen was associated with an 8% incidence of acute reactions including fever, chills, skin, rash, intravascular hemolysis, hypotension, dyspnea and renal failure. Drug-induced antibodies have also been described [5].

This trial was performed to determine if the tolerance to the drug could be improved with a five-day schedule as compared to a weekly schedule. The study was undertaken as part of the new drug program of the Early Clinical Trials Group of the EORTC.

MATERIALS AND METHODS

All patients selected for this trial had histologically confirmed solid malignancies no longer suitable for conventional therapy and an expected survival of at least 6 weeks. They had completely recovered from major toxic effects induced by prior treatments. All patients had white blood cell counts (WBC) of at least 3500/mm^3 and all but one had platelet counts of 100,00/mm^3 or more. Eligibility criteria included maximum serum creatinine and bilirubin levels of 1.5 mg/100 ml, but some patients with creatinine levels between 1.5 and 2.0 mg/100 ml were entered at dosages $\leq$ 45 mg/m^2/day. Routine history, physical examination, blood cell counts and SMA 12 chemistries were obtained

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weekly. Antitumor activity was evaluated according to WHO criteria [6].

Therapy consisted of a 60–120-min infusion of HME daily for 5 consecutive days. Courses were repeated every 3 weeks. The duration of infusion was based on previous experience indicating that shorter infusion times might produce tachycardia and shortness of breath [2]. The drug was supplied by Labaz, S. A., Brussels, as a lyophilized powder that was reconstituted with sterile water for injection. The appropriate dose was diluted in 150–500 cc of dextrose 5% in water. Drug administration was followed by an infusion of 150 cc of fluid over 2 hr to maintain a venous access in the event of acute toxic effects.

RESULTS

Twenty-three patients were entered into the study, 8 men and 15 women (Table 1). Their median age was 60 yr, with a range of 32–73 yr, and their median performance status (Karnofsky) was 60, with a range of 40–80. All patients had received prior chemotherapy (3 patients), radiotherapy (2 patients) or both (18 patients). All patients had solid tumors, mainly breast and non-small cell lung carcinomas.

The starting dose was based on existing clinical data and not, as currently recommended, on 1/10 of the LD_{10} in mice [7]. Daily doses of 15, 30, 45, 60 and 80 mg/m^2 were evaluated. Three to 6 new patients were entered at each dose level. Eleven patients received one course, 9 received two courses and the remaining patients received 3–4 courses for a total of 40 courses. Up to the daily dose of 45 mg/m^2, patients were re-treated at higher doses when no significant toxic effects were encountered in previous courses.

Table 1. Pretreatment characteristics

Total entered	23
Male/female	8/15
Median age (range)	60(32–73)
Median performance status (range)	60(40–80)
Prior radiotherapy	2
Prior chemotherapy	3
Prior radio- + chemotherapy	18
Tumor types	
breast	7
lung (non-small cell)	4
cervix	2
cylindroma	2
miscellaneous	8

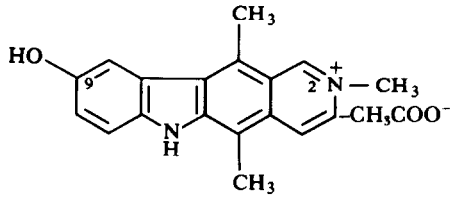

Fig. 1. Chemical structure of 9-hydroxy-2N-methyl-ellipticinium acetate.

Response to therapy was difficult to assess since most patients had no measurable lesions. However, one patient with extensively pretreated breast cancer achieved partial response in skin lesions. Unfortunately, she developed carcinomatous meningitis after two courses of HME and ultimately died of her disease. Another woman with advanced breast cancer had transient minor regression of cutaneous lesions, while liver involvement remained unchanged.

Only minimal myelosuppression was encountered, with lowest WBC and platelet counts of 2500/mm^3 and 98,000/mm^3 respectively (Table 2). Among patients with WBC $\geq$ 4000/mm^3 upon entry in the trial, only 3 had lower counts with chemotherapy, i.e. 1 at 60 and 2 at 80 mg/m^2/day. There was no evidence of hemolysis, infection or treatment-related hemorrhage.

Dryness of the mouth and phlebitis at the injection site were the major toxic effects of HME (Table 3). Dryness of the mouth was dose-related and dose-limiting. Patients complained of this effect within a few days after initiation of therapy and it could last for several weeks. Some improvement could occasionally be obtained with pilocarpine chlorhydrate. Dryness of the mouth was first noted in 1 out of 5 patients at a daily dose of 30 mg/m^2. At the next higher dose level it was severe in 2 patients who had moderate renal function impairment, and it was accompanied by bilateral swelling of the submaxillary glands in 1. At a dose of 80 mg/m^2/day, dryness of the mouth was experienced by all patients and resulted in difficulties in speaking and eating for most of them.

Localized but painful phlebitis was another major side effect which occurred at daily doses of 30 mg/m^2 or higher. This was generally first apparent at the end of a course and could develop thereafter. All patients who did not receive HME through a central venous catheter at doses $\geq$ 60 mg/m^2/day experienced phlebitis. This effect could not be alleviated by larger dilutions in up to 500 cc or prolonged drug administrations of up to 2 hr.

Other non-hematologic toxic effects were essentially mild to moderate. Gastrointestinal distress consisting of nausea and vomiting, flat stools and/or diarrhea was noted at all dose

Table 2. Drug-induced myelosuppression

Dosage mg/m²/day × 5	No. of evaluable patients/ No. of evaluable courses	Median nadir × 10^3/mm³ WBC	Platelets
15	3/3	4.0 (4.0–4.6)	191 (180–240)
30	4/5	7.2 (3.8–8.6)	198 (115–300)
45	4/8	3.4 (2.7–4.7)	146 (140–155)
60	5/9	3.5 (2.5–6.8)	150 (140–290)
80	4/6	4.5 (2.8–6.2)	170 (98–334)

Table 3. Non-hematologic side effects

	Dosage (mg/m²/day) 15	30	45	60	80
No. of evaluable courses	3	7	8	10	7
No. of evaluable patients	3	5	4	5	5
No of toxic patients	1	4	4	5	5
Dryness of mouth	—	1	3(2)*	5(2)	5(4)
Phlebitis	—	3	3	3(2)	4(3)
Nausea and vomiting	1	2	4(1)	4	5
Diarrhea	—	2	4(1)	3	4
Stomatitis	—	1	—	1(1)	2
Fever	—	2	—	—	—
Weakness	—	—	1	1	—
Renal	—	—	—	1	1
Hepatic	—	—	—	—	1
Alopecia	—	—	—	—	1
Chest pain	—	—	—	—	1

*( ) = No. of patients with severe toxic effects.

levels and did not require any specific measures. The remaining adverse reactions were rare and mostly negligible; they included stomatitis, fever, weakness, transient renal and hepatic impairment, alopecia and chest pain during drug infusion. Nephrotoxicity occurred in 2 patients/3 courses and consisted of rapidly reversible elevations of serum creatinine levels to 1,7, 2.0 and 2.7 mg/100 ml respectively. No other toxic effects were found in this study.

DISCUSSION

Detection of drug efficacy is infrequent in phase I trials. Patients entered in these studies are generally heavily pretreated, they often receive short-term therapy at suboptimal doses and may lack clearly evaluable lesions. Despite these facts, antitumor activity was demonstrated in two patients with breast cancer, confirming previous observations [2–4].

With the daily times five schedule, dryness of the mouth and local phlebitis clearly emerge as the major toxic effects of HME. The comparison of our findings with published data on weekly administrations suggests that the relative importance of individual adverse effects might vary according to the schedule. Qualitatively, however, drug-induced toxic effects are similar and, of special interest, myelosuppression remains negligible. The previously reported acute reactions possibly related in the past to drug-induced antibodies were not observed in this trial. This apparent benefit could be accounted for, at least in part, by the low incidence of these reactions, the small number of entries in the study and the small number of courses per patient. The total dose that may be given per course is similar for both a weekly and a 5-day schedule. According to our experience, 60 mg/m² seems to be the maximum tolerated daily dose for 5 consecutive days in courses repeated every 3 weeks.

In conclusion, results of this trial are consistent with a schedule dependency of HME-induced toxic effects. However, weekly administrations of the drug might be easier to handle as compared to daily doses.

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