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Short communication

Phase I study of Datelliptium chloride, hydrochloride given by 24-h continuous intravenous infusion

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Summary. Datelliptium chloride, hydrochloride (SR 95156B, NSC 626718X, DHE) was studied in a phase I trial of escalating doses given on a single 24-h continuous intravenous infusion schedule. Doses were escalated from 40 to 500 mg/m^2 in 19 patients who received a total of 24 courses. Courses were repeated after a minimal interval of 3 weeks. Local venous toxicity occurred at low doses ($\leq$100 mg/m^2) and was circumvented by the use of a central venous access for higher doses. Other clinical adverse events occurred ($\geq$330 mg/m^2), including moderate nausea and vomiting, mild diarrhea, dry mouth, neuropsychiatric manifestations, and fatigue. All of these side effects were reversible and none was dose-limiting. The dose-limiting toxicity was related to hepatic laboratory-test abnormalities in the form of reversible elevations of levels of serum bilirubin and liver enzymes at doses of $\geq$330 mg/m^2. The maximum tolerated dose for this schedule is 500 mg/m^2. Hematologic toxicity was minimal and non-dose-limiting. Neither drug-related deaths nor objective complete or partial responses were observed. However, a minor response and a long-term disease stabilization were obtained.

Introduction

Ellipticine is a natural alkaloid isolated from *Ochrosia elliptica* [12]. Ellipticine-derived compounds constitute an original class of cytotoxic agents. Intercalation into DNA and inhibition of topoisomerase II have been reported to be the main mechanisms of action of these agents [4, 7, 9, 10]. Elliptinium acetate (Celiptium) was the first agent from this class of compounds to be widely tested in the clinical setting; it demonstrated interesting clinical activity in breast cancer [2, 11, 13], although its use was limited due to toxic effects such as antibody-dependent hemolytic reactions [6], severe xerostomia, and gastrointestinal toxicity [2]. Fundamental studies have been carried out in the family of ellipticine-derived compounds with the aim of improving both their activity and their tolerability.

Datelliptium chloride, hydrochloride (SR 95156B, NSC 626718X, DHE) was selected from a new subseries of these compounds due to its good activity in murine tumor models over a broad range of doses [1]. This suggests that Datelliptium could have a higher therapeutic index than Celiptium in the clinical setting. We report the results of a phase I study of Datelliptium given by 24-h continuous intravenous infusion.

Patients and methods

Patients. To be eligible for this study, patients were required to show a confirmed histology of malignant solid tumor or lymphoma, non susceptibility to benefit from other available treatment, an age between 16 and 75 years, a WHO performance status of $\leq$3 (or a Karnofsky score of >40%), and a life expectancy of >2 months. Other eligibility criteria included adequate hematologic and renal functions (WHO grades of 0 or 1), and adequate hepatic function tests (liver enzymes corresponding to WHO grade 0, 1, or 2). Patients had to give their informed consent to participate in the study. Subjects who had previously been treated with Celiptium and patients displaying active bacterial infection, signs of cerebral involvement, or alcohol intoxication were excluded from the study. In addition, patients should not have received radiotherapy or other chemotherapy for a least 4 weeks prior to treatment with the drug under study.

Treatment. Datelliptium [2-(*N, N*-diethylamino-ethyl)-9-hydroxy ellipticinium chloride, hydrochloride; (Fig. 1) was supplied by Sanofi Recherche (Montpellier, France). Escalating doses of Datelliptium were given by a single 24-h continuous intravenous infusion. The drug was diluted in 50 ml isotonic 5% glucose solution and was given by electronic pump to ensure a constant infusion rate. Courses could be repeated at the investigator's discretion in the absence of toxicity after a minimal interval of 3 weeks. The starting dose (40 mg/m^2) was chosen on the basis of available results from other phase I trials using a 1-h infusion regimen [8]. At least two patients were treated and completely evaluated

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SR 95156 B

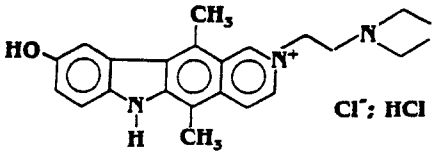

Fig. 1. Molecular structure of datelliptium chloride, hydrochloride (SR 95156B, NSC 626718X, DHE) [2-(*N, N*-diethylamino-ethyl)-9-hydroxy ellipticinium chloride, hydrochloride]

Table 1. Patients' characteristics

	Number of patients
Eligible patients	19
Mean age (range)	60 (37–79) years
Sex (M/F)	9/10
Mean Karnofsky performance status (range)	84% (60%–100%)
Primary tumor:	
Ovarian	4
Melanoma	4
Colorectal	3
Breast	2
Gastric	2
Other[a]	4 (*)
Prior treatment:	
Surgery	17
Radiotherapy	5
Chemotherapy	19
Mean number of prior chemotherapy regimens (range)	3 (1–5)
Metastatic disease	19

[a] 1 nasopharyngeal cancer, 1 cervical cancer, 1 soft-tissue sarcoma, and 1 cancer of unknown primary origin

at each dose before subjects were advanced to the next level following an interval of at least 1 week. For each patient who developed a toxicity of higher than grade 2, a new subject was included, for a maximum of 6 patients per dose level. The study was approved by the hospital's ethics committee.

Pretreatment and follow-up studies. Every treatment course was preceded by a thorough clinical examination, including a history and determinations of weight, body surface area, and performance status. Laboratory safety tests included a complete blood count and determinations of levels of serum electrolytes, blood urea, serum creatinine, proteins, albumin, bilirubin, alkaline phosphatase, SGOT, SGPT, cholesterol, triglycerides, glucose, uric acid, and serum iron. Urinary examination, an EKG, a chest X-ray, evaluations of tumor markers, and other studies to evaluate any tumor target lesions were also done. Clinical examinations and laboratory studies were repeated daily for 3 days and then weekly for 3 weeks; target lesions and/or tumor markers were evaluated on day 21.

Evaluation methods. Both toxicity and antitumor activity were evaluated using the WHO recommendations for reporting results of cancer treatment [5].

Table 2. Laboratory-test anomalies after the 1st course in 19 patients

Dose (mg/m^2)	Number of patients/ courses	WBC	Platelets	Creatinine	Bilirubin	SGOT/SGPT
40	3/5	1G1[a]	2G1[a]	0	1G1[a]	1G1[a] 1G2[a]
60	2/2	1G1[a]	0	0	0	0
100	3/3	0	0	0	0	0
200	2/3	0	0	0	0	1G1
330	7/9	1G2	0	1G1	1G1 2G2	1G1 1G2 2G3
500	2/2	1G1	0	1G1	1G1 1G2[b]	1G2 1G4

G. WHO grade
[a] Anomalies reported as not being related to drug treatment
[b] Associated with clinical jaundice

Results

Our patients' characteristics are shown in Table 1. A total of 19 patients were included (9 men and 10 women). The mean age of our patient population was 60 years (range, 37–79 years). All 19 patients had metastatic disease and had undergone prior chemotherapy.

Tolerability of the first course

Mild nausea and vomiting (grade 1 or 2) was reported by 8 individuals (42%). Among the 19 patients who completed the 1st course, 4 developed grade 1 diarrhea (21%) and 4 experienced mild dry mouth. Neurologic side effects occurred in 6 subjects (32%) in the form of excitability, confusion, depression, tremors, or muscular cramps; the majority of these side effects was reported at the highest doses (330 and 500 mg/m^2). Local venous toxicity occurred in 3 patients at doses of ≤ 100 mg/m^2, but this was circumvented by the use of a central venous access for drug delivery in patients treated at higher doses. Other less common clinical side effects included intense but reversible fatigue, mild headache, anorexia, and grade 1 paresthesia. There was no drug-related death, mucositis, or alopecia.

The laboratory-test results are reported in Table 2. Hematologic toxicity was mild, with a maximum of grade 2 leukopenia being observed in one patient (nadir on day 8 or 15, with complete recovery occurring on day 21). Two cases of grade 1 elevation of serum creatinine levels occurred at the two highest doses on day 3 or day 8, with complete recovery occurring on day 15 or 21. The dose-limiting toxicity was a consistent, reversible rise in serum bilirubin values and/or liver enzymes at doses of 330 and 500 mg/m^2, which was observed on day 2 or 3; recovery to baseline values occurred on day 15 or 21. Mild alkaline phosphatase anomalies (grade 1 or 2) were encountered in ten patients but were not clearly dose-related.

Tolerability of subsequent courses

Only five subsequent courses were given to four patients. Neither signs of cumulative toxicity nor new clinical or biologic anomalies were observed in these subjects.

Antitumor activity

A total of 15 patients had evaluable disease as judged by target lesions, biological markers, or both. One subject with cervical cancer showed a minor response (200 mg/m^2) and in another patient, a progressive metastatic resistant rhabdomyosarcoma (330 mg/m^2) stabilized. No objective partial or complete response was observed. It should be noted that all of our patients had been heavily pretreated (a mean of three prior chemotherapy regimens), and most of them completed only one course of treatment, making evaluation of antitumor activity difficult.

Discussion

Apart from local venous toxicity at doses of ≤ 100 mg/m^2, both the clinical and biologic tolerability of Datelliptium were excellent at doses of up to 200 mg/m^2. Local venous toxicity was overcome by the use of central venous access. Starting at 300 mg/m^2, consistent clinical side effects occurred in the form of nausea and vomiting, diarrhea, dry mouth, intense fatigue, and neuropsychiatric manifestations. However, all of these effects were only mild to moderate and readily reversible. The absence of mucositis and alopecia is noteworthy. The myelosuppression caused by Datelliptium is minimal, making it an interesting candidate for combination chemotherapy with myelotoxic drugs. The dose-limiting toxicity manifested as a rise in levels of serum bilirubin and liver enzymes of grade ≥ 2 at 330 mg/m^2 (3/7 subjects) and 500 mg/m^2 (2/2 patients). These changes occurred rapidly after drug administration (day 2 or 3), and all were reversible by day 21.

Of the five patients who developed grade ≥ 2 hepatic toxicity, three had hepatic metastases. This might be a risk factor due to either impaired biliary elimination or impaired hepatic metabolism of the drug. Fluorescence microscopy on rat-tissue cryosections has shown that the drug is taken up by mitochondria; the fluorescent mitochondrial filament staining observed on primary hepatocyte cultures transformed into granulations after drug incubation, offering a possible explanation for the observed hepatotoxicity [3].

In conclusion, the maximum tolerated dose of Datelliptium chloride, hydrochloride (SR 95156B) given on a single 24-h continuous intravenous schedule is 500 mg/m^2. The dose-limiting toxicity was a reversible rise in levels of liver enzymes and serum bilirubin at doses of 330 and 500 mg/m^2, especially in patients with hepatic metastases. The recommended dose for further phase II studies using this schedule would be 330 mg/m^2, with dose reduction being carried out in case of hepatic test anomalies, which should be carefully monitored. However, since a higher total dose/cycle can be more safely achieved using the 1-h infusion $\times$ 3-day schedule [8], the 24-h continuous-infusion regimen is not recommended for further phase II trials of this drug.

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