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CLINICAL TRIAL REPORT

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Phase I study of RP 49532A, a new protein-synthesis inhibitor, in patients with advanced refractory solid tumors

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Abstract Giroline (RP 49532A) is a new protein-synthesis inhibitor with broad antitumor activity in experimental models. In the present phase I study, Giroline was given by 24-h i. v. infusion every 3 weeks at doses ranging from 3 to 15 mg/m^2 to 12 patients with advanced refractory solid tumors. The dose-limiting toxic effects were delayed hypotension and severe asthenia. The maximum tolerated dose (MTD) was 15 mg/m^2. Transient nausea and vomiting during infusion were reported at all dose levels. Mild reversible prolongation of prothrombin time and activated partial thromboplastin time was observed in most patients at dose levels above 3 mg/m^2. No antitumor activity was observed. The toxicity profile of Giroline precludes further evaluation in cancer patients.

Key words Protein-synthesis inhibitor · Chemotherapy
Phase I study

Introduction

Inhibitors of protein synthesis represent an original class of anticancer drugs. RP 49532A {Giroline; (15,25)-3-amino-1-[4-(2-amino-1H-imizadolyl)]-2-chloropropanol·2HCl} is a new marine compound isolated from the sponge *Pseudaxinyssa cantharella* collected in New Caledonia [1, 4]. In preclinical screening tests, Giroline exhibited significant antitumor activity in vitro against both murine leukemic P388 cells with acquired resistance to doxorubicin and human solid-tumor cell lines and in vivo against several grafted murine tumors [1]. In biochemistry studies, Giroline has been shown to inhibit protein synthesis without affecting transcription [5]. The 10% lethal dose (LD_{10}) in mice was 30 mg/m^2 following a single i. v. dose and 4 mg/m^2 per day in a 5-day study. Histological examinations showed hepatic steatosis, rhabdomyolysis, and testicular cytotoxicity. The proposed initial dose for human studies was one-tenth of the LD_{10} in mice, that is, 3 mg/m^2. We report on a phase I clinical study of Giroline that was conducted at Centre Léon Bérard. The purpose of this study was to determine the toxic effects of Giroline, to define a recommended dose for phase II trials, and to document the antitumor activity of this new compound.

Patients and methods

Patient selection

Patients aged 18–75 years were eligible for this study if they had a histologically confirmed solid malignancy and had exhausted all the standard therapeutic options for their disease. Eligibility criteria included a life expectancy of at least 3 months; a WHO performance status of 0–2; adequate bone marrow, renal, liver function; written informed consent; and no active neuromuscular disease, liver steatosis, uncontrolled systemic infection, or cardiac dysfunction. This study was approved by the Ethics Committee of Claude Bernard University (Lyon).

Study parameters

Prior to therapy, all patients underwent a complete physical examination and a medical history was obtained. Complete blood cell counts, chemistry profiles, prothrombin (PT) and activated partial thromboplastin time (APTT), creatinine level, liver tests, plasma lipids, total proteins, protein electrophoresis, and urinalysis were obtained prior to treatment and at the end of the infusion and were monitored weekly for up to 4 weeks after the end of therapy. Chest X-ray, liver ultrasonography, and electrocardiography (ECG) were performed prior to therapy. ECG was also performed at the end of infusion and prior to each treatment course. Patients had frequent monitoring of their vital signs (hourly during the first 12 h of infusion and at 24 and 48 h after

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This work is dedicated to the memory of Prof. Michel Clavel

Table 1 Patients' characteristics

Characteristics	Number of patients
Patients entered	12
Median age	57 (range, 37–71) years
M/F	5/7
Median performance status	1 (range, 0–2)
Tumor type:	
Breast	4
Head and neck	2
Colorectal	2
Miscellaneous[a]	4
Previous therapy:	
Chemotherapy	12
Radiotherapy	8

[a] Including leiomyosarcoma, bladder carcinoma, adenocarcinoma of unknown origin, and lung carcinoma

infusion). Patients were followed closely for signs of toxicity or other biological effects. Standard WHO criteria for response and toxicity were used. NCI-CTC criteria were used for APTT modifications. A severity score was used in case of events not gradable on the WHO or NCI-CTC scale [6, 8].

Drug formulation and administration

Giroline was supplied by Rhône-Poulenc Rorer in 2-ml vials containing 10 mg of active drug. The required dose was diluted in 50 ml of an isotonic glucose solution and given i.v. with an electric pump over a 24-h period. Courses were repeated every 3 weeks.

Dose-escalation scheme

The initial dose was 3 mg/m^2, i.e., one-tenth of the LD_{10} in mice. Three patients entered the initial dose level. Giroline doses were incremented following a modified Fibonacci escalation scheme until the maximum tolerated dose (MTD) was reached. The MTD was defined as the dose resulting in WHO grade 3 or 4 toxicity in ≥50% of the patients [3, 7]. No intrapatient dose escalation was allowed.

Results

Patient population

A total of 12 patients entered the study. Their characteristics are listed in Table 1.

Dose escalation

Doses were incremented from 3 to 15 mg/m^2. A total of 26 courses were given (median, 2; range, 1–4); all the courses were given according to the protocol except in the case of 1 patient treated at 10 mg/m^2, whose 1st course was delivered by a 30-min i.v. infusion.

Table 2 Adverse reactions related to Giroline

	Giroline dose level			
	3 mg/m^2 (3 patients, 8 courses)	6 mg/m^2 (3 patients, 8 courses)	10 mg/m^2 (3 patients, 7 courses)	15 mg/m^2 (3 patients, 3 courses)
Hypotension WHO grade:				
0	3	2	1	1
1	0	1	2	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	2
Asthenia Severity grade[a]:				
0	1	1	1	0
1	0	0	0	0
2	2	1	2	0
3	0	1	0	3
4	0	0	0	2
Nausea/vomiting WHO grade:				
0	0	0	0	0
1	0	1	0	0
2	2	1	2	0
3	1	1	1	3
4	0	0	0	0

[a] 1, Mild; 2, moderate; 3, severe; 4, life-threatening

Cardiovascular toxicity

The dose-limiting toxicity was hypotension with shock requiring corrective treatment, which was experienced by 2 of 3 patients treated at the 15-mg/m^2 dose level. This hypotension was delayed, dose-related, and slowly reversible. One patient developed grade 4 hypotension (baseline value, 165/90 mmHg; nadir, 85/56 mmHg) at 27 h after the end of the Giroline infusion. Intravenous fluid replacement was required for 24 h before the blood pressure returned to the baseline value. Another patient developed grade 4 hypotension (baseline value, 110/70 mmHg; nadir, 65/45 mmHg) at 48 h after the end of the infusion. Dopamine treatment associated with fluid replacement was required for 4 days before the baseline blood-pressure value recovered. Moreover, grade 1–2 hypotension was observed in 4 of 9 patients who were treated at the 3 lowest dose levels (Table 2). This hypotension regressed within 1–4 days in all patients.

Asthenia

Asthenia was experienced by most patients (9 of 12) at all dose levels, and its severity was dose-related; all patients treated at 15 mg/m^2 complained of severe asthenia. It began on the day of Giroline administration and lasted for 1–20 days (median, 3 days). One patient treated at 15 mg/m^2 who did not experience hypotension was removed from the study after the first course because of severe and protracted asthenia.

Other toxic effects

All patients reported nausea and vomiting, but this side-effect was not dose-limiting. No hematological dose-limiting toxicity was observed. Mild, reversible, and dose-independent leukocytosis was observed in 7 patients (10 courses). Mild and reversible thrombocythemia was recorded in 3 patients. Modifications of PT and APTT were experienced by some patients. Drug-related prolongation of PT ($<60\%$) was observed in 2 patients (4/8 courses) treated at 6 mg/m^2 and in all patients (8/10 courses) treated at the 2 highest dose levels, but it was either mild or moderate. Grade 1 prolongation of APTT was observed in 3 patients (4 courses) treated at the 2 highest dose levels, and grade 2 prolongation was experienced by 1 patient receiving 15 mg/m^2. Determination of inhibiting factors (antithrombin III, plasminogen, protein C) and of activating factors (II, V, VII+X factors) showed a transient decrease in hepatic biosynthesis. One patient treated at 6 mg/m^2 experienced grade 1 cutaneous erythema with burning after the first Giroline administration. Drug rechallenge resulted in recurrence of the skin reaction. Alopecia was mild and infrequent. Myalgia related to Giroline was reported by 1 patient treated at 3 mg/m^2, by 1 patient treated at 6 mg/m^2, and by 2 patients treated at 10 mg/m^2.

Antitumor activity

No antitumor activity was observed.

Discussion

The background for the selection of Giroline for clinical evaluation was its new structure, its experimental antitumor activity, and its mechanism of action. Toxicology studies carried out in mice and dogs did not reveal any major toxic effect that could preclude the drug's administration to cancer patients. In the present phase I trial, the dose-limiting toxicity of Giroline given by 24-h i.v. infusion every 3 weeks was hypotension with shock, and the MTD was reached at 15 mg/m^2. Hypotension was delayed, occurring at 24–48 h after the end of drug administration, and its incidence and severity were dose-related. The physiopathological mechanism of this hypotension remains unknown. Severe asthenia was also a dose-limiting side effect with no clear relation to hypotension. Due to the severity and incidence of the dose-limiting side effects observed during the first course in all three patients treated at 15 mg/m^2, no more patients were entered at that dose level.

A similar toxicity pattern was reported for Giroline in a phase I study of this drug given as a 1-h infusion every 3 weeks. In this trial, hypotension was the dose-limiting toxicity and the MTD was reached at 17 mg/m^2 [2]. Taking into account the results of our study together with the experience of investigators who tested the 1-h infusion schedule, we decided not to pursue further evaluation of this agent due to its unmanageable dose-limiting toxicity.

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References

1. Ahond A, Bedoya Zurita M, Colin M, Fizames C, Laboute P, Lavelle F, Laurent D, Poupat C, Pusset J, Thoison O, Potier P (1988) La Giroline, nouvelle substance antitumorale extraite de l'èponge *Pseudaxinyssa cantharella*. C R Acad Sci [III] 307: 145–148
2. Alakl M, Armand JP, Gandia D, Le Bail N, Bayssas M, Chevalier P, Carde P, Escudier B, Recondo G (1991) Phase I and pharmacokinetics of RP 49532: Giroline in cancer patients. Proc Am Assoc Cancer Res 10: 310
3. Carter SK (1977) Clinical trials in cancer chemotherapy. Cancer 40: 544–557
4. Lavelle F, Fizames C, Ahond A, Poupat C, Curaudeau A (1989) Experimental properties of RP 49532, a new antitumor marine compound. Proc Am Assoc Cancer Res 30: 583
5. Lavelle F, Zerial A, Fizames C, Rabault B, Curaudeau A (1991) Antitumor activity and mechanism of action of the marine compound girodazole. Invest New Drugs 9: 233–244
6. NCI Division of Cancer Treatment (1988). NCI toxicity criteria. National Cancer Institute, Bethesda, Maryland
7. Schneidermann MA (1966) Mouse to man: statistical problems in bringing a drug to clinical trial. In: Proceedings of the 5th Berkeley Symposium on Mathematical Statistics and Probability. University of California Press, Berkeley, pp 855–866
8. World Health Organization (1979) Handbook for reporting results of cancer treatment. Offset publication 48. WHO, Geneva