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Phase I Study of DABIS Maleate Given Once Every 3 Weeks

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DABIS maleate is an alkylating quaternary nitrogen. In a phase I study DABIS maleate was administered as a single intravenous infusion once every 3 weeks. 32 patients with solid tumours were studied, at least 3 per dose level (50–1400 mg/m^2). Dose-limiting toxicity was severe paresthaesias in the face, around the mouth and in the tongue. Cerebellar ataxia developed at 750 mg/m^2 or higher. Haematological toxicity was minimal. Nausea and vomiting were mild to moderate. No other non-haematological side-effects were noted. The recommended dose for phase II studies at once every 3 weeks is 750 mg/m^2 intravenously as a 15 min infusion.
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INTRODUCTION

DABIS MALEATE (1,4-bis(2′-chloroethyl)-1,4-diazabicyclo [2.2.1] heptane dihydrogen dimaleate) (NSC 262666) (Fig. 1) is an alkylating quaternary nitrogen. The quaternary nature of the nitrogen atoms change the alkylating character of the chloroethyl side-chains. This was expected by results in the DNA alkaline elution assay and in studies on DNA interactions. DABIS maleate has different DNA-binding affinities than other nitrogen mustards and shows a different pattern of alkylation in the alkaline elution assay (EORTC-New Drug Development Office [NDDO], data on file).

In the NCI tumour panel, DABIS maleate is active in P 388 leukaemia, CO 26 colon carcinoma, MX-1 breast cancer, MAC 13 colon carcinoma and in the M 5076 sarcoma resistant to cyclophosphamide and other nitrogen mustards. The latter findings seems to confirm a mechanism of action different from classical alkylating agents.

In acute toxicity studies in mice the single intravenous administration of DABIS maleate at the LD_{10} dose of 500 mg/m^2 (176 mg/kg) caused marked but reversible haematological toxicity consisting of reduced reticulocyte count, reduced red blood cells, reduced haemoglobin and decreased lymphocyte counts. Histopathological changes were found in kidney and spleen, consisting of renal tubular necrosis and depletion of the white pulp of the spleen without evidence of recovery.

In subacute studies DABIS maleate was administered at a daily dose of 220 mg/kg intraperitoneally to mice on days 0–4 and 14–18. Marked haematological toxicity as well as various pathological changes were seen in kidneys, liver, spleen, heart, thymus and testicles. The renal abnormalities (tubular necrosis) and testicular changes (atrophic tubules, spermatogenic arrest) were irreversible in contrast to the damage in the other organs.

A single dose of DABIS maleate was administered to rats intravenous at a dose of 8.4 mg/kg (50 mg/m^2) and daily intraperitoneal at a dose of 11 mg/kg (66 mg/m^2) from days 0–4 and 14–18. Only minor and reversible changes in haematological, macroscopic or histopathological examination were observed.

In view of these data, the EORTC-NDDO selected DABIS maleate for clinical studies. We performed a phase I study with a single short-running infusion every 3 weeks.

PATIENTS AND METHODS

Eligibility and follow-up

The study protocol was in accordance with the EORTC guidelines for phase I trials with single agents [1] and was approved by the EORTC Protocol Review Committee. Eligibility criteria included histologically proven progressive cancer, resistant to conventional therapy; life expectancy of at least 2 months; performance score WHO ≤ 2; age 18–75 years; no chemotherapy, immunotherapy or radiotherapy for at least 4 weeks before entry (mitomycin, nitrosoureas and extensive radiotherapy for at least 6 weeks) and recovery from toxic effects of prior treatment; no clinical signs of brain involvement or leptomeningeal disease; white blood cells (WBC) $\geq 4 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l; normal bilirubin and normal renal function. All patients gave written informed consent prior to therapy.

Laboratory tests, including complete blood counts with differential, electrolytes, renal and liver function chemistries, and urinalyses, were repeated weekly while the patients were on study.

Drug formulation and dosage

DABIS maleate was supplied by the EORTC-NDDO. DABIS maleate has been formulated as a sterilised solution in distilled

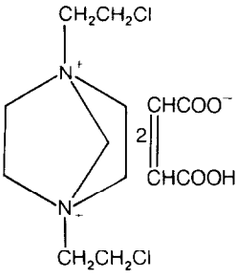

Fig. 1. The structure of DABIS maleate.

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Table 1. Patients' characteristics

No. of patients	32
Males/females	15/17
Age median (range)	48 (21–73)
WHO performance score	
Median	1
Range	0–2
No. of patients with:	
No previous therapy	5
Previous radiotherapy	13
Previous chemotherapy	25
Previous immunotherapy	3
Primary tumour	
Adenocarcinoma of colon and rectum	8
Adenocarcinoma of unknown primary	4
Adenocarcinoma of the pancreas	4
Adenocarcinoma of the stomach	3
Adenocarcinoma of the breast	3
Mesothelioma	3
Renal cell cancer	2
Miscellaneous	5

water. Each vial contains 2.2 ml of this solution (50 mg/ml). Diluted in 5% dextrose at 2 mg/ml and 8 mg/ml, the drug is stable for at least 48 h in normal light. In solution, the (diluted) drug is not adherent to glass or infusion bags/systems (EORTC-NDDO data on file and ref. 2).

The starting dose was 50 mg/m^2, which represents 1/10 of the LD_{10} in mice [2]. DABIS maleate was administered as 5–15 min intravenous infusion. Dose escalation was performed according to the modified Fibonacci scheme. At least 3 patients were studied at each dose level, at non-toxic dosis interpatient dose excalation was allowed. Cycles were repeated every 3 weeks. Patients were scheduled to receive at least two cycles of DABIS maleate.

RESULTS

32 patients were entered in the study. Patients' characteristics are given in Table 1. A total of 74 evaluable cycles was administered. There were no drug-related deaths. The dose levels studied were 50, 100, 200, 400, 600, 750, 900, 1200 and 1400 mg/m^2. Only minimal haematological toxicity was observed; leucocytopenia grade 1 in 5, grade 2 in 1 and thrombocytopenia grade 1 in 2 of the 74 cycles, which was not related to dose level. No treatment-related anaemia occurred.

The dose-limiting side-effect of Dabis maleate was neurotoxicity, consisting of paresthesias and cerebellar ataxia (Table 2). The paresthesias were localised in the face, around the mouth and in the tongue. Paresthesias, directly following infusion, were first noted at a dose of 200 mg/m^2. At doses of 400–750 mg/m^2 the paresthesias were mild, grade 1, lasting from less than 1 h to 48 h. Severe paresthesias were observed at doses of 900–1400 mg/m^2 lasting from 1 day to more than 28 days. Ataxia with unsteadiness of gait and ataxia of the extremities with disturbed finger–nose test and heel–knee test were observed at doses of 750–1400 mg/m^2. These symptoms were mild at doses of 750 mg/m^2 and lasted from 1 to 4 days. At a dose of 900–1400 mg/m^2 the ataxia interfered with normal daily activities and lasted from 1–21 days. The neurological signs were reversible in all patients. No abnormalities were found in spinal fluid or on computed tomography (CT) of the brain, which were performed in 2 and 5 patients, respectively.

Table 2. Neurotoxicity

Dose (mg/m^2)	Patients (1st dose level)	Evaluable cycles	WHO grade 1	2	3	4
50	3 (3)	7	0	0	0	0
100	4 (3)	11	0	0	0	0
200	6 (3)	10	1P	0	0	0
400	3 (3)	7	0	0	0	0
600	3 (3)	7	4P	0	0	0
750	6 (5)	17	13P (6A)	0	0	0
900	6 (6)	10	6P	3A	–	0
1200	2 (1)	2	1P	1P	2A	0
1400	5 (5)	5*	3P (1A)	2P	2A	0

P = paresthesias, A = ataxia.
*For 2 patients ataxia could not be evaluated properly.

Nausea and vomiting was mild to moderate and lasted from 2–8 h. It appeared to be independent of the dose (Table 3) and it could not be prevented with standard antiemetic therapy. Short-lasting hypotension grade 1 was measured in nine cycles at the two highest dose levels only. No renal toxicity, alopecia or other organ toxicity was observed.

Tumour responses were not seen. 1 patient with a mesothelioma had a regression of more than 50% of a skin metastasis, but progressed at other sites.

DISCUSSION

From the NCI screening panel, DABIS maleate emerged as an interesting alkylating agent. In animal studies DABIS maleate, in contrast to most other cytotoxic drugs, showed activity in the MAC 13 colon carcinoma and was active against the M 5076 sarcoma resistant to cyclophosphamide and other nitrogen mustards, which suggests a mechanism of action different from classical alkylating agents. Based on animal toxicity studies myelotoxicity and nephrotoxicity was expected, while no other significant toxicities, especially no neurotoxicity was observed [2].

This phase I study demonstrated that neurotoxicity is the dose-limiting toxicity in man. The distribution of paresthesias around the mouth, tongue and later spreading the face suggest a central origin of the neurological symptoms with involvement of the trigeminal nuclei in brainstem. The simultaneous presence of unsteadiness of gait and ataxia of the extremities point to a

Table 3. Nausea and vomiting

Dose mg/m^2	Patients (1st dose level)	Evaluable cycles	WHO grade 1	2	3	4
50	3 (3)	7	0	1	0	0
100	4 (3)	11	0	6	0	0
200	6 (3)	10	1	5	0	0
400	3 (3)	7	1	6	1	0
600	3 (3)	7	1	5	0	0
750	6 (5)	17	7	3	0	0
900	6 (6)	10	1	9	0	0
1200	2 (1)	2	1	1	0	0
1400	5 (5)	5	2	3	0	0

cerebellar origin as there were no associated sensory signs in the extremities. Thus Dabis maleate seems to exert its neurotoxic influence on the level of the brainstem or cerebellum although the exact mechanism is unknown. The neurological signs were dose-related (Table 2) and always reversible.

Nausea and vomiting occurred at each dose level, but symptoms were mild to moderate and short lasting. Myelosuppression was negligible and no nephrotoxicity, alopecia or other organ toxicities have been observed.

If the once every 3 weeks schedule is to be used for phase II studies, the recommended dose is 750 mg/m^2 as a 15 min intravenous infusion, repeated every 3 weeks. Other schedules are presently under investigation.

1. EORTC New Drug Development Committee. EORTC guidelines for phase I trials with single agents in adults. *Eur J Cancer Clin Oncol* 1985, **21**, 1005–1007.
2. Dabis maleate. TNO-CIVO Institute Report no 87.187/27302, 87.194/27302, 87.346/27302, 87.262/27302.

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Phase II Study of Teniposide in Patients with AIDS-related Kaposi's Sarcoma

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Antitumour activity of cytotoxic agents, evaluated in patients with AIDS-related Kaposi's sarcoma (KS), is about 30–80%. However, responses are mostly partial and short. Experience with etoposide is similar. Teniposide has a longer elimination half-life and superior antitumour activity compared with etoposide in some experimental models. Thus a phase II trial was done in 25 patients with AIDS-related KS. Teniposide was given by 60-min infusion at 360 mg/m^2 every 3 weeks. 10 (40%) showed a partial response, median duration of 9 (6–20) weeks. The main side-effects were leukopenia, thrombocytopenia, nausea and vomiting, alopecia and mucositis.
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INTRODUCTION

DUE TO the risk of significant myelosuppression and opportunistic infections, cytotoxic therapy should be used with caution in patients with AIDS-related Kaposi's sarcoma (KS). As a rule, this approach has been only indicated in patients failing to less aggressive approaches, or in having aggressive cutaneous disease, visceral involvement and/or rapid tumour progression with systemic B symptoms [1]. Vinblastine, vincristine, bleomycin, methotrexate and doxorubicin have been often used in this disease, either as single agents or as part of combination regimens [5, 6]. Objective responses to these agents ranged from 30–80% in various studies, being usually of short duration and with no clear impact in patient overall survival [2, 3].

Clinical experience with podophyllotoxin derivatives in AIDS-related KS has been restricted to trials with etoposide [4–6]. Objective responses to this agent have been around 30–50%, with no clear impact on the natural history of the disease. Considering that teniposide has a longer elimination half-life and superior antitumour activity compared to etoposide in some experimental models [7, 8], a phase II trial of this agent was performed in patients with AIDS-related KS.

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PATIENTS AND METHODS

This study was performed at the AIDS and Oncology Unit of Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil. Patients were eligible for the study if they had the histopathological diagnosis of KS and clinical and laboratorial features compatible with the diagnosis of AIDS, including confirmatory serological tests for the presence of HIV infection. The patients had to be classified as stage II-IV AIDS-related KS, according to Krigel's classification (NYU) criteria [6, 9]. The other eligibility criteria were a performance status (WHO) between 0–3, life expectancy of at least 3 months, no evidence of active infection and no prior exposure to chemotherapy. Prior to entry in the trial, patients had to undergo a complete medical history, physical examination, blood counts, lymphocyte counts, including B and T (helper and suppressor) subpopulations, HIV serology, routine biochemistry, urinalysis and culture of the urine, chest X-rays, abdominal ultrasound, endoscopy and computed tomography (CT) (according to indication in individual cases). The number of CD4 + cells was not required for admission in the study due to logistic reasons. The characteristics of patients included in the trial are summarised in Table 1. Teniposide was administered by a 60-min intravenous infusion at the dose of 360 mg/m^2 in 250 ml 5% dextrose solution every 3 weeks. Prophylactic antiemetic therapy was allowed in the study and consisted of metoclopramide 1 mg/kg given over a 5–10 min intravenous infusion 30 min before the administration of teniposide. None of the patients had prior or concomitant zidovudine therapy. Toxic effects and objective responses