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.

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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

Table 1. Patient characteristics

No. of patients	25 (all male)
Homosexuals	22
Intravenous drug users	3
Age (years)	28 (26–39)
Performance status (WHO)	2 (0–3)
Stage of disease (Krigel's classification)	
IIA	6
IIB	6
IIIA	6
IIIB	3
IVA	0
IVB	4
Sites of disease	
Skin only	9
Skin/mucosa/lymph nodes	12
Skin/viscera	4
Viscera only	0
Medium number of chemotherapy cycles	2 (1–4)

were reported according to the WHO criteria, using only objective evaluation of marker lesions measurable bidimensionally. Patients were considered evaluable for both toxicity and response if they received at least one cycle of teniposide.

RESULTS

In this trial, patients received median of 2 (1–4) cycles of teniposide. The main side-effects were leukopenia, thrombocytopenia, nausea and vomiting, alopecia and mucositis. These adverse effects and the corresponding grades are presented in Table 2. 5 patients showed evidence of disease progression after one cycle of teniposide. Another 2 patients died due to *Pneumocystis carinii* infection, which was confirmed by transbronchial lung biopsy after one cycle of therapy. In another case, the patient developed signs of peritonitis at day 11 of the first cycle of teniposide and died of septic shock. Necropsy revealed the occurrence of intestinal perforation at the site of a responding sarcomatous lesion. Objective responses were documented in 10/25 (40%) patients. Responses were observed at various sites such as the skin, gastrointestinal tract, and oral cavity. These responses were all partial and with a median duration of 9 weeks (6, 7, 8, 8, 8, 10, 12, 12, 12, and 20 weeks, respectively). Eventually, all patients died due to progressive disease and/or opportunistic infections.

DISCUSSION

The management of patients with AIDS-related KS should be based upon the clinical and laboratorial evidences of immunosuppression, performance status, and the extent of disease involvement [1, 2]. Outside experimental trials, patients with only a few cutaneous sarcomatous lesions may be followed symptomatically, without specific antitumour therapy [6]. This patient population should be offered the participation in clinical trials, specially those exploring new approaches to stimulate the immune system, and lacking significant bone marrow toxicity [9]. Localised lesions should be preferably managed by surgical excision or radiation therapy. Patients with cutaneous and/or lymph node envolvement but indolent clinical course might benefit from immunologycal approaches and/or single agent non-myelosuppressive chemotherapy. The use of biological response modifiers, such as interferons, has received special attention in recent years. Studies with high-dose alpha-2 recombinant interferon have produced objective responses in 30–50% of the cases. However, these responses have been mainly documented in patients with limited disease, without opportunistic infections and showing high T4:T8 lymphocyte ratio [10, 11]. Occasional complete responses have been observed in patients with over 100 CD4 + cells/mm^3 and cutaneous involvement only. In patients with opportunistic infections and/or B symptoms, the response rates tend to drop to 10–20%. More recently, encouraging results have been demonstrated with alpha-2 interferon plus zidovudine [12].

Table 2. Side-effects in patients receiving teniposide

Type	No. of cycles/event (%)	Grade (WHO) 1	2	3	4
Leukopenia	57/57 (100)	7	22	20	8
Thrombocytopenia	27/57 (47)	9	7	10	1
Nausea and vomiting	26/57 (46)	10	11	4	1
Alopecia	25/57 (44)	6	11	8	–
Mucositis	20/57 (35)	8	8	4	–
Paresthesias	9/57 (16)	6	3	–	–
Dizziness	6/57 (11)	3	1	2	–

The main difficulty of chemotherapy in patients with AIDS-related KS rests on the risk of enhancing immunosuppression. Therefore, these agents should only be given in the routine in more aggressive cases. Indeed, the observation of significant antitumour activity with various agents, such as vinca alkaloids, etoposide, bleomycin or doxorubicin, has to be balanced against their short duration of responses and the risks of severe infectious complications. Recently, partial or complete responses have been reported in 13/18 patients with AIDS-related KS treated with a 6-drug regimen, including doxorubicin, vinblastine, bleomycin, actinomycin D, vincristine and dacarbazine (ABV/ADV). However, tumour responses were of short duration and all patients subsequently died of opportunistic infections [13]. In our phase II trial, teniposide showed objective antitumour activity in 40% of the patients. Unfortunately, responses were all partial and of short duration. These results are comparable to those observed with the other podophyllotoxin derivative, etoposide, given as a single agent [4–6]. Although symptomatic relief was demonstrated in some patients, it is very difficult to attribute a meaningful long-term benefit due to the drug in our patient population. Therefore, it is not yet clear whether teniposide as a single agent would add significantly to the drugs available against AIDS-related KS. The observation of bone marrow toxicity in all patients does not suggest a major role for this agent as part of combination chemotherapy regimens for the treatment of this disease. Further studies in patients with AIDS-related KS should focus on the evaluation of novel therapeutic approaches aiming not only at the eradication of the tumour, but also at influencing the process of tumour initiation and promotion and the complications resulting from HIV-dependent immunosuppression.

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Resistance Modification by PSC-833, a Novel Non-immunosuppressive Cyclosporin A

Peter R. Twentyman and Norman M. Bleehen

A novel non-immunosuppressive cyclosporin A, PSC-833, has been tested for its ability to circumvent resistance to doxorubicin, vincristine and colchicine in human and murine multidrug resistantant (MDR) cell lines. This compound is shown to be a highly potent resistance modifier, being 7–10-fold more potent than the parent compound, cyclosporin A, whilst approximately equal to cyclosporin A in the growth inhibitory effects of compound alone. Reversal of the P-glycoprotein-associated MDR drug accumulation defect is a major component of resistance reversal for PSC-833, as it is for cyclosporin A.
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INTRODUCTION

AGENTS THAT can reverse multidrug resistance (MDR) have entered clinical trial over the last few years [1–4]. The lead compound, verapamil, although dose-limited by its cardiac toxicity, has been reported to produce positive effects in drug-resistant myeloma patients [1]. A search for improved resistance-modifiers has resulted in the identification of several compounds which are more potent than verapamil. Among these is the immunosuppressive agent, cyclosporin A [5] which has a particularly high binding affinity to P-glycoprotein, the drug efflux "pump" molecule frequently overexpressed in MDR cells [6]. The immunosuppression brought about by cyclosporin A is a disadvantage for its use as a resistance modifier and we examined the relationship between immunosuppression and resistance modification for a number of cyclosporin A analogues [7, 8]. Among naturally-occurring cyclosporins, we found a close relationship between the two properties [7], but we found that chemically-modified cyclosporins could be non-immunosuppressive whilst being highly effective resistance modifiers [8]. One non-immunosuppressive compound, O-acetyl cyclosporin A (B3-243) was approximately 4-fold more potent that cyclosporin A in the human small cell lung cancer MDR subline H69/LX4 [8]. The effectiveness of O-acetyl cyclosporin A as a resistance modifier was subsequently confirmed by others [9]. We subsequently found, however, that in mouse cell lines with low P-glycoprotein expression, the potencies of O-acetyl cyclosporin A and cyclosporin A were equal and that, in lines with high P-glycoprotein expression, cyclosporin A was superior [10].

Studies carried out at Sandoz have now led to the availability of PSC-833, a novel cyclosporin A analogue, which is a lead compound for clinical trial as a resistance modifier [11]. In this paper we describe our initial findings regarding the effectiveness of PSC-833 in a variety of *in vitro* model systems.

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MATERIALS AND METHODS

Cell lines

We used two pairs of parent and MDR cell lines in these studies. The human small cell lung cancer line NCI-H69/P was originally obtained from Drs D. Carney and A. Gazdar of the NCI/Navy Medical Oncology Branch, Bethesda, Maryland, USA. The MDR subline NCI-H69/LX4 was derived in this laboratory by *in vitro* growth in doxorubicin and maintained in 0.4 μg/ml of this agent [12, 13]. Subline H69/LX4 expressed