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Etoposide for Epidemic Kaposi's Sarcoma: a Phase II Study

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Abstract—*Fourteen untreated patients with epidemic Kaposi's sarcoma stages III and IV were treated with etoposide* 150 mg/m^2 *on* 3 *consecutive days every* 4 *weeks. No responses were observed. Myelosuppression was severe with white blood count WHO grade* 3–4 *in nine patients and with platelets WHO grade* 3–4 *in one patient. Three patients developed opportunistic infections during therapy. It is concluded that etoposide is inactive in epidemic Kaposi's sarcoma.*

INTRODUCTION

EPIDEMIC Kaposi's sarcoma or AIDS-related Kaposi's sarcoma differs in many respects from classical cases or from the African form [1]. Epidemic Kaposi's sarcoma has a much worse prognosis with early dissemination, visceral involvement and a high 2-year mortality [2]. The most important novel aspect is, however, the high frequency of opportunistic infections. These infections have a bearing on antineoplastic therapy as aggressive use of chemotherapy may further diminish the immune response potentially increasing the rate of opportunistic infections and shortening survival.

The first systemic chemotherapy trials in epidemic Kaposi's sarcoma were started in 1981. Since then, a number of trials on single agents or combination chemotherapy have been published. The podophyllintoxin etoposide (VP16-213) is reported to be one of the most active single agents with relatively good subjective tolerance. Etoposide was utilized for the less advanced forms of the disease. In one study of 41 patients treated with etoposide, 30% achieved a complete remission and 46% a partial remission [3]. The majority of these patients had early stage disease. Toxicity was acceptable with a moderate myelosuppression. However, 12% of patients treated developed opportunistic infections during therapy.

Because of these promising results in early stage disease a phase II trial with etoposide was initiated in patients with Kaposi's sarcoma.

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MATERIALS AND METHODS

Patients with histologically proven measurable and progressive Kaposi's sarcoma stage III or IV were entered in the trial. Measurable disease was defined as a known mass that could be clearly measured by physical examination or with ultrasound or CT scan. Patients were excluded from the study in the following circumstances: severe intercurrent infection, abnormal liver function (WHO grade 1), impaired haematologic status (WBC $<3.0 \times 10^9$/l or platelets $<75 \times 10^9$/l) or severe impairment of activity level (ECOG performance status 3 or 4). Verbal informed consent was obtained from the patients. Stage and symptom status were assigned using a new staging system proposed by Krigel *et al.* [4] (Table 1). Staging procedures included chest radiographs, CT scan or ultrasound of the abdomen, endoscopy of the upper and lower gastrointestinal tract.

Bronchoscopy was performed only in the presence of chest X-ray abnormalities or pulmonary symptoms. Physical examination was performed every 4 weeks. Routine laboratory studies were performed weekly and included complete blood cell counts with differentials and blood chemistry serum creatinine, albumin, SGOT, SGPT, LDH, bilirubin and alkaline phosphatase and γ-glutamyltransferase. Patients received etoposide 150 mg/m^2 in 500 ml of 0.9 NaCl during a 60 min infusion on 3 consecutive days. Treatment was given every 4 weeks in case of full haematological recovery, otherwise treatment was postponed 1 week. Dose adjustments were made according to white blood cell and platelet nadirs: for grade 2 and 3 toxicity dose reduction to 75% and 50% respectively. Response and toxicity

Table 1. Staging system for Kaposi's sarcoma

Stage	Characteristics
I	Cutaneous, locally indolent
II	Cutaneous, locally aggressive with or without regional lymph nodes
III*	Generalized mucocutaneous and/or lymph node involvement
IV	Visceral
Subtypes	
A	No systemic signs or symptoms
B	Systemic signs > 10% weight loss for fever > 100°F (37.5°C) orally unrelated to an identifiable source of infection lasting >2 weeks

*Generalized = more than upper or lower extremities alone.

Table 2. Patient characteristics

Evaluable patients	14
Median age (years)	39
Performance status (ECOG scale)	0–1
Stage:	
III A	10
III B	3
IV A	1
IV B	0
Opportunistic infections prior to therapy	1

evaluation was assessed according to WHO criteria [5].

Patients had to receive at least two courses of treatment in order to be evaluable for response. Treatment was continued until objective evidence of disease progression, unacceptable toxicity or patient refusal.

RESULTS

Fourteen patients were entered into the study. All patients were evaluable. The patient characteristics are shown in Table 2. The mean number of administered cycles was 2.7 (range 2–5). There were no complete or partial remissions. Nine patients experienced no change. Three of these received only two courses of chemotherapy. Five patients had progressive disease during treatment. The haematological toxicity was severe. The mean white cell count on day 14 was 1.9 (range 0.8–4.6) $\times 10^9$/l. the mean platelet count on day 14 was 112 (range 46–241) $\times 10^9$/l. Three patients developed an opportunistic infection with pneumocystic carinii during treatment. All three responded to antibiotics. Two additional patients had short periods of unexplained fever. No toxic deaths due to infection were observed. Six patients experienced mild gastrointestinal toxicity (nausea WHO grade 1) and all had alopecia (WHO grade 3).

DISCUSSION

Our patient characteristics are not different from those reported in the literature and contained mainly early stage disease of Kaposi's sarcoma. Dose and schedule of etoposide are identical to those used in other studies [3]. However, in contrast to earlier reports, we were unable to demonstrate any activity of etoposide in epidemic Kaposi's sarcoma using WHO criteria. Even if we used such criteria as flattening of lesions, lightening of colour, or resolution of edema, as has been used in other studies, no responses were seen.

Although the haematological toxicity was considerable the rate of opportunistic infections during treatment appeared to be not different from that reported from the literature and is in accordance with the natural course of AIDS.

It is concluded from this study that etoposide has no therapeutic activity in epidemic Kaposi's sarcoma.

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