Pergamon

European Journal of Cancer, Vol. 34, No. 7, pp. 1131–1132, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10156-3

Short Communication

A Phase II Study of DaunoXome® in Advanced Urothelial Transitional Cell Carcinoma

S.D. Fosså,[1] N. Aass[1] and G. Parö[2]

[1]Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, 0310 Montebello, Oslo, Norway; and [2]Swedish Orphan AB, Stockholm, Sweden

Liposomal encapsulation of anthracyclines is claimed to reduce toxicity and to improve pharmacokinetics. Therefore, 15 patients with locally advanced or metastatic transitional cell cancer (TCC) of the urinary tract were entered into a phase II study assessing the response rate (WHO criteria) and toxicity of DaunoXome® 100 mg/m^2 given as a 1 h infusion every third week. During treatment, 6 patients remained stable and 8 had progressive disease. 1 patient died of pulmonary embolism after the first cycle and was not evaluable for response. No patient developed grade 4 myelotoxicity. Grade 3 leucopenia was seen in 5 patients and grade 1 thrombocytopenia in 1 patient, with no treatment-related changes of biochemical liver and kidney function tests. 4 patients complained of angina pectoris-like chest pain during the initial phase of the first or second infusion. The event was associated with a decrease in systolic blood pressure by 20–30 mm in 1 patient leading to permanent treatment discontinuation. In the other 3 and all subsequent patients, intramuscular application of 100 mg hydrocortisone 1 h prior to DaunoXome® infusion prevented similar hypotensive reactions. In this study, intravenous (i.v.) DaunoXome® 100 mg/m^2 every third week showed no anticancer activity in advanced TCC.

Key words: DaunoXome®, urothelial TCC, hypotensive reaction
Eur J Cancer, Vol. 34, No. 7, pp. 1131–1132, 1998

INTRODUCTION

ANTHRACYCLINES SUCH as doxorubicin and epirubicin have shown moderate efficacy in advanced urothelial and prostate cancer with response rates of approximately 20% [1]. The side-effects (myelosuppression, cardiotoxicity and nausea/vomiting) have, however, represented dose-limiting factors in these often elderly patients. Scher and Norton [1] have suggested a dose-relationship for anthracyclines in bladder cancer. Liposomal encapsulation of anthracyclines is claimed to reduce toxicity and to improve pharmacokinetics [2]. The active drug is selectively accumulated in the tumour tissue [3], thus theoretically enabling the application of higher doses of anthracyclines without increasing toxicity. DaunoXome® (NeXstar) (liposomal encapsulation of daunorubicin) given at doses of 100–120 mg/m^2 is reported to cause acceptable gastrointestinal and cardiac toxicity and has been effective in anthracycline-sensitive malignancies, in particular in Kaposi's sarcoma [4, 5]. Therefore, an early phase II study was designed to assess the response rate and the toxicity of DaunoXome® in advanced transitional cell carcinoma (TCC) of the urinary tract.

PATIENTS AND METHODS

Patients with advanced histologically verified and measurable urothelial TCC received DaunoXome® 100 mg/m^2 as a 1-h infusion, repeated every 3 weeks. To be eligible for the study, patients had to have had no prior systemic chemotherapy, a Karnofsky performance status > 70 and display adequate hepatic, renal and bone marrow function. The cardiac ejection fraction had to be $\geq$45%. Indicator lesions measurable by computer tomography had to be at least 2.5 cm to allow reproducible measurements.

Response was evaluated after two cycles according to the WHO criteria. In cases of acceptable tolerability, patients with response or stable disease continued until progression, whereas treatment was discontinued after two cycles in cases

Correspondence to S.D. Fosså.
Received 15 May 1997; revised 2 Nov. 1997; accepted 10 Dec. 1997.

of progressive disease. In patients who progressed before two cycles, 'early progression' was recorded.

Haemoglobin, leucocytes and platelets were measured weekly during treatment. Dose modifications were made based on haemoglobin, leucocytes and platelet counts on day 1 of each scheduled cycle.

All patients gave their informed consent. The protocol was approved by the Ethical Committee of Health Region II in Norway.

RESULTS

Patients

From January 1994 to October 1995, 15 patients (13 males, 2 females, mean age: 68 years) were entered into the study. None of the patients had previously received radiotherapy or cytotoxic chemotherapy. One patient was strictly ineligible as subsequent review of his histological slides revealed a 2 cm previously undetected renal cell carcinoma which had been removed completely by nephrectomy performed for a large urothelial cancer of the renal pelvis. As the biopsy from his indicator lesion (lymph node metastases) showed urothelial TCC, he remained in the analysis for response. The patients displayed the following indicator lessons: primary tumour (4 patients); lung metastases (4 patients); lymph node metastases (6 patients); skin metastases (1 patient).

Treatment

A total of 35 cycles were given. 2 patients received only one cycle, 9 had two cycles, 1 patient three cycles, and 3 patients had four cycles.

Response

One patient was not evaluable for response as he died of pulmonary embolism 1 week after the first DaunoXome® infusion. Another patient developed inoperable ileus after the first cycle, due to abdominal metastases (early progression). No further chemotherapy was given to this patient. None of the remaining evaluable 13 patients receiving at least two cycles achieved an objective response. Progression was recorded in 7 patients. 6 patients displayed stable disease after two cycles. 1 patient with stable disease had progression after the third cycle and 3 patients after two further DaunoXome® applications. In the remaining 2 patients with stable disease, treatment was discontinued after the second cycle due to patients' request and to side-effects (see below).

Toxicity

During the initial phase of the trial, angina pectoris-like chest pain associated with a decrease in systolic blood pressure by 20–30 mm was experienced by 4 patients. The symptoms developed during the first 10–20 min of the first (3 patients) or second (1 patient) DaunoXome® infusion. The symptoms subsided spontaneously in 3 patients after stopping the infusion transiently. They did not re-occur when the patients received 100 mg hydrocortisone 1 h before the second cycle. However, in 1 patient, treatment was discontinued permanently as after the start of the second cycle he experienced a severe hypotensive reaction. Subsequently all patients received 100 mg hydrocortisone (Solu-Cortef®, Pharmacia-Upjohn) 1 h before the DaunoXome® infusion which prevented a hypotensive reaction in further patients.

Grade 4 leucopenia was not observed in any of the 15 patients. 5 patients developed grade 3 leucopenia, whereas no more than grade 1 thrombocytopenia was observed (1 patient). No treatment-related changes of biochemical liver and kidney function tests were encountered. 4 patients suffered from moderate nausea and vomiting for 2–3 days after their DaunoXome® applications, controllable by anti-emetics. Only 1 patient developed grade 1 alopecia.

DISCUSSION

There seems to be no substantial activity of DaunoXome® in advanced urothelial TCC. This disappointing result is probably due to the fact that daunorubicin has no notable antitumour effect in this malignancy. The mild haematological toxicity seen in these elderly patients indicates that higher doses of DaunoXome® would have been tolerable.

In 4 patients, angina pectoris-like chest pain and hypotension were observed. Similar adverse events have been reported in other studies [4] and occur usually during the first 10–15 min of an infusion. The aetiology of this side-effect is unclear, but release of vasoactive mediators from the liposomal component has been suggested. The symptoms usually subside when the infusion is discontinued or slowed down. It has, therefore, been suggested [4] that the infusion time be increased to at least 2 h. The prophylactic application of corticosteroids, as used in the present study and other studies [6], may also avoid or reduce this type of toxicity. We strongly recommend regular supervision of the patients during the infusion. In individual patients, permanent discontinuation of DaunoXome® infusion may become necessary.

In conclusion, DaunoXome® at doses of 100 mg/m^2 every third week appears not to be active in advanced bladder cancer, but is well tolerated by the patients and causes only slight or moderate biochemical or haematological toxicity. The application of higher doses of DaunoXome® seems possible and should be further investigated in patients with daunorubicin-sensitive malignancies. DaunoXome® should be given by infusions of at least 2 h and should be preceded by corticosteroid application, in order to prevent drug-related angina pectoris-like chest pain combined with hypotensive episodes.

1. Scher HI, Norton L. Chemotherapy for urothelial tract malignancies: breaking the deadlock. *Semin Surg Oncol* 1992, **8**, 316–341.
2. Forssen EA, Ross ME. DaunoXome treatment of solid tumors: preclinical and clinical investigations. *J Liposomal Res* 1994, **4**, 481–512.
3. Gabizon AA. Selective tumor localization and improved therapeutic index of anthracyclines encapsulated in long-circulating liposomes. *Cancer Res* 1992, **52**, 891–896.
4. Gill PS, Wernz J, Scadden DT, *et al.* Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 1996, **14**, 2353–2364.
5. Presant CA, Scolaro M, Kennedy P, *et al.* Liposomal daunorubicin treatment of HIV-associated Kaposi's sarcoma. *Lancet* 1993, **341**, 1242–1243.
6. Uziely B, Jeffers S, Isacson R, *et al.* Liposomal doxorubicin: antitumor activity and unique toxicities during two complementary phase I studies. *J Clin Oncol* 1995, **13**, 1777–1785.