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Short communication

Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter

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Summary Fourteen patients with previously treated, locally advanced/metastatic transitional cell carcinoma (TCC) of the bladder or ureter received paclitaxel at a dose of 200 mg m^{-2} administered as a 3-h infusion every 21 days. The activity of paclitaxel in this group of patients was modest. The response rates were one partial response (PR) (7%) and three stable disease (SD). There were two early deaths.

Keywords: paclitaxel; bladder cancer; transitional cell carcinoma

Cisplatin and methotrexate are generally regarded as the most active single agents in the treatment of transitional cell carcinoma (TCC) of the bladder (Scher and Norton, 1992) and form the cornerstone of most commonly used chemotherapy combinations.

However, patients with poor performance status (PS), significant weight loss or significant hepatic or pulmonary metastases do not often benefit from aggressive combination chemotherapy regimens. Renal impairment quite often coexists in this setting and is a further complicating factor limiting the use and effectiveness of many chemotherapeutic agents.

Paclitaxel has already demonstrated quite significant single-agent activity in ovarian and breast cancer (McGuire et al, 1989; Seidman, 1995), while, at the same time, having a favourable toxicity profile. In vitro studies (Rangel et al, 1994; DeHaven et al, 1995), as well as early results from a phase II study in previously untreated patients with advanced bladder cancer (Roth et al, 1994), suggest quite significant activity in this disease. Data from a study in which paclitaxel was used either as salvage therapy or in patients with renal impairment (Dreicer et al, 1996) were encouraging, although the number of patients was very small.

We therefore decided to assess the response and toxicity to single-agent paclitaxel in patients with previously treated, locally advanced/metastatic TCC of the bladder or ureter.

PATIENTS AND METHODS

Patient characteristics

In a three-centre open phase II study, 14 patients with advanced bladder or ureteric TCC with measurable or evaluable disease received single-agent paclitaxel. Their clinical characteristics are shown in Table 1.

Prior treatment regimens and responses for these patients are shown in Table 2. All patients received one treatment regimen before paclitaxel.

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Staging and follow-up

Before treatment, all patients had full history and complete physical examination, full blood count (FBC), urea and electrolyte estimation (U and Es), liver function tests (LFTs), electrocardiogram, chest radiography and computerized tomography scan of the abdomen and pelvis or ultrasound, as well as bone scan if symptoms warranted this.

Response to treatment was assessed every two cycles, unless there was evidence of disease progression in the meantime. The standard WHO criteria were used for evaluation of toxicity and response. The presence or absence of localized pain and haematuria were specifically noted.

Treatment

Paclitaxel (200 mg m^{-2} was dissolved in 1 l of 0.9% normal saline and was administered intravenously over 3 h. All patients received dexamethasone 20 mg p.o. (12 and 6 h before paclitaxel administration), chlorpheniramine 10 mg i.v. and cimetidine 300 mg i.v. 30 min before treatment. Treatment was repeated every 3 weeks.

Table 1 Clinical characteristics

Age range (years) (median)	40–73 (68)	
M:F	9:5	
Performance score (ECOG)		
0	3	
1	7	
2	4	
Histology		
Transitional cell carcinoma	13	
Mixed squamous/transitional cell carcinoma	1	
Serum creatinine range (μmol l^{-1}) (median)	70–330 (95)	
Locally advanced disease	4	
Metastatic disease	11	(Four lung/liver, two lung, two liver, one peritoneal, one bone, one bone/lymph nodes)

Table 2 Treatment received prior to paclitaxel

	Treatment		
Response	**Cisplatin-based chemotherapy**	**Alkylating agent-based chemotherapy**	**Radiotherapy**
CR	–	–	1[a]
PR	3	–	1
PD	5	1	–
Adjuvant treatment	1	1	1
Total	9	2	3

[a]This patient received a combination of cisplatin-based chemotherapy and radiotherapy. CR, complete response; PR, partial response; PD, progressive disease.

The dose, infusion rate and schedule of paclitaxel was chosen on the basis of previous phase II and III trials in ovary, breast and lung cancer patients, (Murphy et al, 1993; Eisenhauer et al, 1994; Seidman, 1995).

The study was approved by the ethics committees of the three hospitals that took part. All patients gave written informed consent.

RESULTS

Toxicity

Severe (grade 3/4) haematological toxicity was seen in 23 out of 42 courses, and two patients developed neutropenic sepsis requiring admission to hospital and administration of intravenous antibiotics. The first patient also developed grade 3/4 mucositis. The other patient developed grade 3 peripheral neuropathy.

No other grade 3/4 non-haematological toxicity was noted apart from alopecia which was universal. Toxicity was not related to renal impairment.

Response

The median follow-up was 54 days (range 1–240). A partial remission of 7.4 months was achieved in 1 of the 14 patients (7%) (95% CI 2–12%). This patient had lymph node and bone metastases which had previously responded to a combination of cisplatin, vincristine and methotrexate. Stable disease in patients previously progressing was seen in a further three (21%) patients. The three patients with disease stabilization noticed relief of pain/haematuria for 54–164 days (range). Two patients died within 7 days of treatment and were therefore not assessable for response. The first patient died in hospital from complications related to lung metastases. The second patient deteriorated rapidly while at home and died of unknown cause but is presumed to have had a treatment-related death.

DISCUSSION

Treatment of advanced/metastatic TCC in this group of elderly and often frail patients poses a particularly difficult clinical problem. Single-agent paclitaxel has the distinct advantage of not being dependent upon renal excretion for its elimination (Keung et al, 1993; Schilder et al, 1994) when used in a group of patients who frequently have low creatinine clearance. The patients with moderate renal impairment in the study, as well as two previously untreated patients with severe renal impairment (serum creatinine > 400 umol l^{-1} treated off study (data not shown), did not have enhanced toxicity when treated with paclitaxel.

Paclitaxel was of low efficacy in these relapsed patients, with only one patient responding (7%, 95% CI 2–12%). This was in a poor prognosis group of patients who were pretreated with one chemotherapy regimen in addition to radiation therapy in three cases. Some of them had poor PS, as well as multiple metastatic sites (Table 1). The patient who responded and those who had disease stabilization all had had cisplatin-sensitive disease in the past, whereas those with primary chemotherapy resistance did not respond.

Paclitaxel cannot be recommended for further investigation in platinum-unresponsive TCC, but its activity is being further evaluated in newly diagnosed patients with bladder cancer.

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