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Original Paper

Accelerated Cisplatin-based Chemotherapy for Advanced Bladder Cancer

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The toxicity and efficacy of accelerated cisplatin, vincristine and methotrexate was assessed in patients with advanced urothelial carcinoma. 30 consecutive patients were entered into a phase II trial and treated with cisplatin, vincristine and methotrexate given every 10 days (MOPq10) for four cycles, followed by two further cycles at 21 day intervals. Five complete responses and 14 partial responses were observed (overall response rate 63%; 95% confidence interval 45–78%). The median progression-free survival was 7.5 months (range 1.8–28) and the median overall survival 10.5 months (range 2–36). Toxicity was moderate with no treatment-related deaths. It is concluded that although the overall survival is still disappointing, the toxicity is less with the protocol than reported with methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) or escalated M-VAC (E-MVAC) and the time on treatment is shorter. MOPq10 provided palliative benefit to two-thirds of patients with advanced transitional cell carcinoma including those in their eighth decade.

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INTRODUCTION

METHOTREXATE AND cisplatin are the two most active single agents in the treatment of metastatic bladder cancer [1]. Methotrexate, vincristine and cisplatin (MOP) was introduced in this unit for patients unfit for the more intensive MVP (methotrexate, vinblastine, cisplatin) regimen of Harker and colleagues [2]. Initially, a 21 day cycle was used. Although a lack of significant myelosuppression was seen, the response rate was disappointing.

One of the most important variables related to the use of chemotherapy involves dose and dose intensity. In many cases, combination programmes significantly compromise the ability to deliver adequate doses of each of the most active single agents. In other solid tumours, such as ovarian cancer, a correlation between dose intensity of cisplatin and survival has been suggested in retrospective analyses, and in a randomised trial in testis cancer there was a significant improvement in survival as the cisplatin dose intensity increased from 17.5 to 30 mg/m^2/week. However, no further advantage was seen when the dose intensity was further increased [3–6]. This suggests that a minimum threshold dose intensity exists for cisplatin. With this background, we initiated a phase II trial to increase the dose intensity and contract the time the patient has to undergo cytotoxic therapy by accelerating the frequency of drug administration, giving all three agents every 10 days (MOPq10).

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PATIENTS AND METHODS

Between September 1991 and December 1993, 30 consecutive patients with metastatic or locally advanced cancer of the urothelium were treated with an accelerated cisplatin-based protocol at the Royal London Hospital, U.K. All patients were required to have histologically proven urothelial cancer, measurable tumour on physical examination, chest roentgenogram or computerised tomographic (CT) examination of the chest, abdomen or pelvis, no prior systemic chemotherapy, creatinine clearance more than 40 ml/min and adequate haematological parameters (white blood cell (WBC) count > 3000/μl, platelets > 100 000/ml). All patients with locally advanced disease (T2–T4) must have relapsed after previous radical radiotherapy (RT) to the bladder.

Poor performance status (PS) did not exclude patients from entering the study. All patients were assessed initially by a physical examination, haematological and liver function tests, serum creatinine and 24 h urinary creatinine clearance, chest roentgenogram, CT examination of the abdomen and pelvis, and bone scan if alkaline phosphatase (ALP) was increased or symptoms suggested bone secondaries. Patients who had not had prior cystectomy and only had locally advanced disease following radiotherapy, had a cytoscopy and bimanual examination under general anaesthetic.

Treatment comprised methotrexate 60 mg/m^2 and vincristine 2 mg followed 18 h later by cisplatin 60 mg/m^2. All patients received hydration with 3 l 0.9% normal saline with cisplatin. The first four cycles of cytotoxics were administered every 10 days and this was followed by a further two cycles at 21 day intervals with methotrexate and vincristine given on day 10

(Table 1). If the total WBC on day 10 was <2500/μl or platelet count <100 000/μl, chemotherapy was delayed until haematological recovery. All patients with hydronephrosis, pleural effusion or ascites received folinic acid 15 mg 6 hourly for four doses, 24 h after methotrexate administration. Patients who developed more than grade 1 mucositis also received folinic acid with the subsequent cycles of chemotherapy. Patients came off trial if grade 3 toxicity or a reduction in creatinine clearance to <40 ml/min occurred.

All patients, including those who could only tolerate one cycle of chemotherapy (due to toxicity or disease progression) or who died within 1 month of chemotherapy, were assessable for response, toxicity, dose intensity and survival.

Complete clinical remission (CR) denoted disappearance of all evidence of disease by physical, radiographical and cytological (if indicated) examination for at least 4 weeks. Partial clinical remission (PR) denoted 50% or more reduction in the product of two dimensions of all measurable disease that lasted at least 4 weeks.

Progression-free survival was calculated from the beginning of therapy until clinical or radiological progression or death. Survival was measured from the beginning of treatment to the date of last follow-up or death. Survival and progression-free survival were estimated using the method of Kaplan and Meier [7]. Dose intensity for the first four cycles of treatment is calculated by determining the total number of mg/m^2 of cisplatin given throughout the first four cycles of treatment for each patient. The denominator is then determined by counting the total number of days between the date of the first treatment and 21 days after the date of the fourth treatment. The total number of days of treatment for that patient is then divided by seven to give the number of weeks, and this is used as the denominator to determine the patient's received dose intensity in mg/m^2/week [8].

RESULTS

Between September 1991 and December 1993, 30 consecutive patients were entered into this phase II trial. All 30 patients were considered assessable. Patients' characteristics are listed in Table 2. 16 patients had measurable metastatic disease and 14 had measurable locally advanced disease (6 patients with T4 tumours extending to the pelvic wall on CT scan, 4 patients with T2–T3 tumours identified as muscle-invasive tumours on CT scan, 2 patients with tumours invading the prostate on CT scan, and 2 patients with T4 tumours invading the penis). All patients with locally advanced disease had previously received radical radiotherapy (RT) to the bladder and progressed or relapsed. Median time between RT and starting chemotherapy was 28 months (range 5–74). A further 8 patients with metastatic cancer had previous radical RT to the bladder with a median interval between RT and entering this trial of 7 months (range 5–54).

The median 24 h urine creatine clearance prior to cytotoxic therapy was 68 ml/min (range 48–94). The median age for all patients was 63.6 years (range 36–83). 6 patients were below 60 years of age, 14 were in their 60s, 9 in their 70s and 1 patient was 83 years old. 7 patients were asymptomatic prior to starting cytotoxic therapy (WHO PS = 0), 15 patients had a PS of 1, 6 patients a PS of 2 and 2 patients a PS of 3. 9 patients received at least one cycle of treatment with folinic acid rescue (15 mg 6 hourly for four doses, starting 24 h after methotrexate administration).

Table 1. Drug schedule

	Cycle								
	1	2	3	4	5		6		
Methotrexate (60 mg/m^2)	1	10	19	28	37	49	58	70	80
Oncovin (2 mg)	1	10	19	28	37	49	58	70	80
Cisplatin (60 mg/m^2)	2	11	20	29		50		71	

Values given are days into the treatment.

Table 2. Patients' characteristics

	Number (%)		Responses (%)
Total No. of patients	30		19 (63)
Male/female	22/8 (73/27)		
Site of primary			
Bladder	28	(93)	18 (64)
Renal pelvis/ureter	2	(7)	1 (50)
Histology			
Transitional cell carcinoma	24	(80)	16 (67)
Transitional and squamous cell	5	(17)	2 (40)
Squamous cell carcinoma	1	(3)	1 (100)
Sites of disease			
Locally advanced (T+/N0, M0)	14	(47)	9 (64)
Previous radiotherapy	14		
Metastatic (N+ and/or M+)	16	(53)	10 (63)
Previous radiotherapy	8		
Metastatic sites			
Lung	5	(17)	4 (80)
Liver	1	(3)	0
Bone	7	(23)	5 (71)
Soft tissue	1	(3)	1 (100)
Nodal	7	(23)	4 (57)

Response

Five (16.7%; 95% confidence interval 7–33%) CR and 14 (46.7%; 95% confidence interval 30–64%) PR were seen after chemotherapy, for an overall response rate of 63% (95% confidence interval 45–78%). The response rate for patients with locally advanced disease was 64% and for patients with metastatic disease 62.5%. 4 patients went on to have a cystectomy (one pathological CR and one pathological PR) and all 4 are currently alive and disease-free. The overall median progression-free survival was 7.5 months (range 1.8–28), and the median survival time 10.5 months (range 2–36). Patients with locally advanced disease survived significantly longer than those with distant metastasis (median 15 versus 8.5 months; $P = 0.003$) (Figure 1).

Toxicity

Table 3 summarises the mild degree of toxicity observed with no treatment-related deaths. Haematological toxicity as reflected by median WBC nadir and episodes of neutropenic sepsis was mild with 9 patients with grade 3/4 neutropenia and 4 patients with grade 4 sepsis. 2 patients developed grade 3 mucositis and 1 patient developed grade 3 peripheral neuropathy which improved after 3 months. No patient developed more than grade 2 nephropathy. In 22 patients the degree of alopecia was documented and in only 5 (23%) did more than grade 2 alopecia occur.

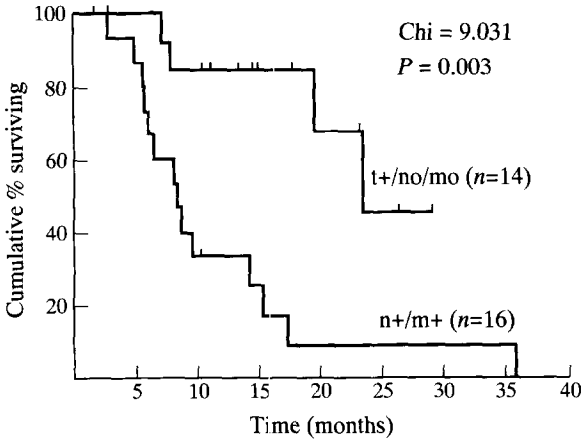

Figure 1. Overall survival by TNM stage.

Dose intensity

A total of 131 cycles of chemotherapy were administered to 30 patients. 21 (70%) patients received four or more cycles of chemotherapy and 13 (43%) completed the scheduled six cycles of therapy (4 patients were scheduled to receive only four cycles prior to cystectomy, chemotherapy was discontinued in 8 patients who did not respond after four cycles and in 5 cases therapy was stopped due to toxicity). The median cumulative dose of cisplatin was 280 mg/m^2 (range 120–480) and for methotrexate 350 mg/m^2 (range 120–780). The mean dose intensity for cisplatin was 27 mg/m^2/week in the 21 patients who received a minimum of four cycles of therapy.

DISCUSSION

We treated 30 patients with advanced bladder cancer with the MOPq10 regimen and achieved a high dose intensity for one of the most active drugs in bladder cancer (cisplatin 27 mg/m^2/week), a low drug-related morbidity and a response rate of 63% with a median duration of 7.5 months.

It is now 17 years since the original report on combination chemotherapy with cisplatin, doxorubicin and cyclophosphamide (CISCA) for advanced cancer of the urothelium [9]. Combination chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) has been compared in randomised trials with CISCA and with single-agent cisplatin and shown to significantly improve both response and survival [10, 11]. Today, M-VAC is considered the most effective protocol for advanced bladder cancer. However, the toxicity associated with this protocol is significant and in the intergroup study only 24% of patients received full-dose M-VAC without dose modifications and 4% drug-related deaths were reported [11].

One method proposed to improve outcome is to increase the administered dose or dose intensity of currently available agents by either increasing the individual doses or decreasing the interval time between cycles of cytotoxics. In contrast to other groups who have used granulocyte colony-stimulating factors (G-CSF) to escalate the drug doses within the M-VAC protocol (E-MVAC) [12–14], we have increased the dose intensity of one of the most active agents, cisplatin, by decreasing the treatment interval rather than increasing the total dose or adding the more myelotoxic agents, vinblastine and doxorubicin. Although data on single-agent vincristine in bladder cancer is lacking, the importance of vincristine dose intensity in breast cancer has been shown [15].

The Eastern Cooperative Oncology Group (ECOG) treated 35 patients with E-MVAC (median age 69 years), 60% of whom responded (17% CR). However, the median duration of response was only 4.6 months, the regimen was associated with significant

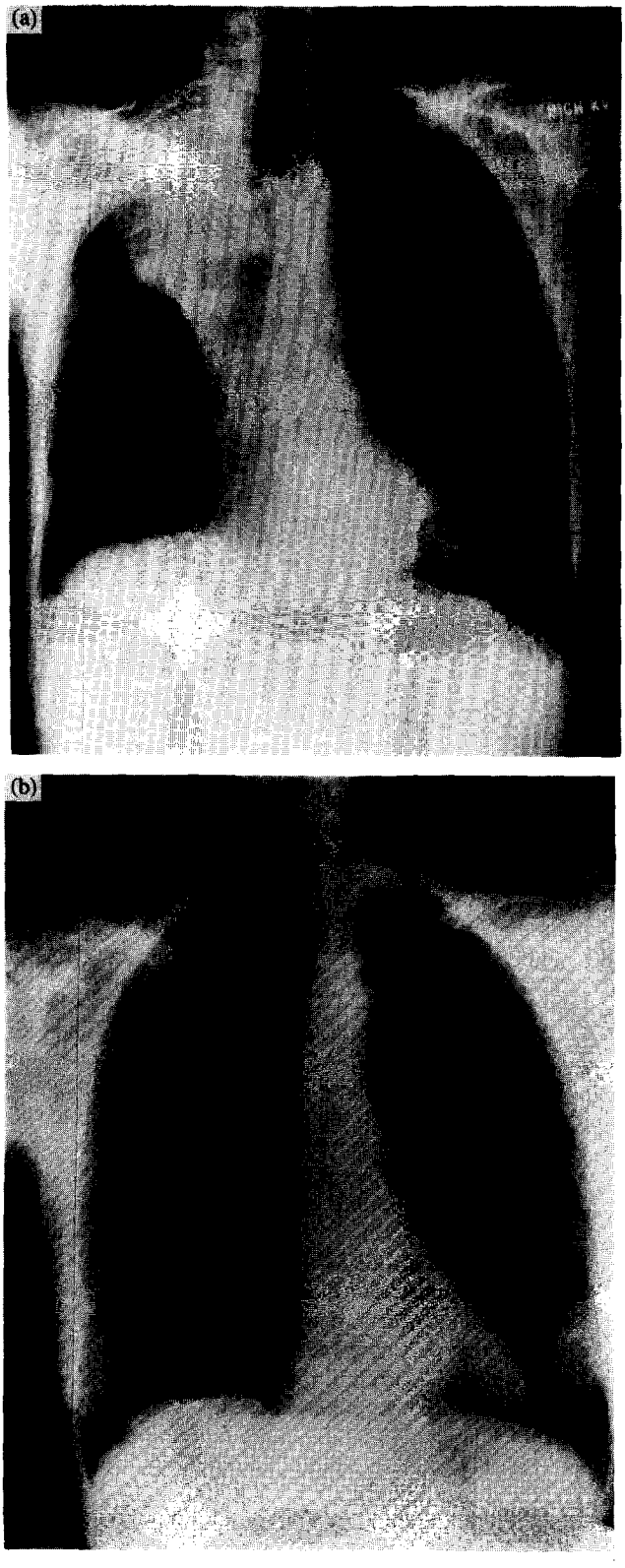

Figure 2. (a) Chest X-ray from a 64-year-old woman (performance status = 3 prior to starting cytotoxic therapy) with histologically proven squamous carcinoma of the renal pelvis. (b) Chest X-ray after completion of four cycles of MOPq10 showing a good partial response and performance status of 0.

Table 3. Toxicity

WBC nadir (× 10⁹/l)	
Median (range)	3.1 (0.3–5.6)
Neutropenic sepsis/number of cycles	5/131 (4%)
Serum creatinine (mmol/l)	
Median pretreatment (range)	118 (78–236)
Median post-treatment (range)	152 (98–240)
Mucositis (*n*)	
Grade 1	20 (67%)
Grade >1	4 (13%)
Peripheral neuropathy (*n*)	
Grade 1	9 (30%)
Grade >1	2 (7%)

toxicity and 8 patients (23%) died of treatment-related causes [12]. The Memorial Sloan-Kettering Cancer Centre (MSKCC), U.S.A. reported a 69% response rate in 16 patients with measurable disease treated with E-MVAC. Of a total of 23 patients treated with E-MVAC at the MSKCC, 58% had at least one episode of neutropenic fever, and vascular and thrombolic events occurred in 26% of patients [13]. The results of the European Organization for Research and Treatment of Cancer (EORTC) phase III trial comparing M-VAC and E-MVAC are eagerly awaited. Despite the high number of patients in our trial who had previously received RT to the pelvis (73%), haematological toxicity was mild and this translated into a low admission rate for neutropenic sepsis.

The planned dose intensity for cisplatin in the M-VAC protocol is 17.5 mg/m²/week, however, the delivered dose of cisplatin over four cycles in a retrospective analysis of 132 patients treated at the MSKCC was only 14.6 mg/m²/week for cycle one, and decreased to 12.6 mg/m²/week in cycle four [16]. This is on the lower end of the dose rate versus dose response curve for cisplatin in urothelial, ovarian and testicular cancers [3]. A dose intensity of 19.6 mg/m²/week has been achieved with E-MVAC [13]. The mean cisplatin dose intensity achieved with MOPq10 (27 mg/m²/week) approaches the 30 mg/m²/week considered to be the optimal dose on the dose rate–response curve for cisplatin [3]. However, the results achieved with this protocol are unlikely to be better than standard M-VAC or E-MVAC. In particular, the relatively small number of complete remissions (16%) similar to that found in the intergroup study in which 13% CRs were observed with M-VAC, makes it unlikely that we will influence survival. In the intergroup study, only 4% of patients remained continuously disease free from 8.5 to 39.5 months of follow-up [11].

The key to improving long-term survival is to increase the proportion of patients achieving a CR. It is unlikely that this goal will be achieved with our current approaches of dose intensification of the most commonly used agents. Given the high response rate (42%) reported in a phase II trial with paclitaxel in previously untreated patients [17], using this agent in combination protocols should be a future direction for research. The combination of vinblastine, ifosfamide and gallium nitrate has also shown significant activity (response rate 68%), and needs further investigation [18].

Currently, for most patients with advanced urothelial carcinoma, MOPq10 with its low toxicity and 63% response rate offers reasonable palliation with a contraction of time on chemotherapy (six cycles can be completed in 91 days compared with 168 days for M-VAC), thus increasing the "chemotherapy-free" survival time.

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