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Original article

A phase II study of mitomycin, fluorouracil, folinic acid, and irinotecan (MFI) for the treatment of transitional cell carcinoma of the bladder

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Abstract

Background and objectives: Cisplatin-based chemotherapy is standard care for metastatic transitional cell carcinoma (TCC) of the urinary tract. However it is not appropriate for all patients, particularly those with poor renal function. There is no clear consensus on the optimal regimen for these individuals or for those after cisplatin failure. Here we present data using mitomycin, 5-fluorouracil, and irinotecan (MFI) in these patients.

Materials and methods: Patients with TCC, who had either received cisplatin-based chemotherapy previously or who were not deemed fit for cisplatin therapy (creatinine clearance was less than 60 ml/min) were eligible for treatment with the experimental combination chemotherapy regimen MFI.

Results: Thirty-six patients were treated with MFI between 2001 and 2004. Overall response rate was 19% and median overall survival (OS) was 5.4 months (95% CI 3.3–8.4 months). The response rate and overall survival in both groups was 19% and 5.4 months, respectively, (95% CI 2.9–7.1 months) in the pretreated and 2.5– 9.3 months in the untreated. The most common toxicity was malaise (grade 3 or 4 = 28%).

Conclusions: MFI appear to be a combination which requires further investigation in patients where cisplatin and gemcitabine are not applicable.

Keywords: Bladder cancer; Mitomycin; Camptothecin analogues; Fluorouracil; Antineoplastic agents

1. Introduction

Metastatic transitional cell carcinoma (TCC) of the urinary tract is associated with a poor survival. Cisplatin is considered to be the most active single agent in TCC with response rates of 15%–30% [1–3]. Improved survival is seen with combination chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) compared with cisplatin alone [4] or with cyclophosphamide, doxorubicin, and cisplatin [5]; overall response rates of up to 71% have been seen with MVAC chemotherapy with a median survival of greater than 1 year [6]. However, long-term survival is poor. In addition, this regimen produces substantial toxicity including a reported treatment-related mortality of up to 4% and neutropenic sepsis in over 10% of patients [6].

Newer protocols have achieved similar results with less toxicity. Treatment with an accelerated regimen of vincristine, methotrexate, and cisplatin, at our institution, was found to have similar efficacy to MVAC with less toxicity [7]. A phase III study, comparing MVAC with gemcitabine and cisplatin, found similar response rates and survival, but less toxicity, in the gemcitabine-cisplatin arm [8].

Treatment options remain limited in patients who cannot receive cisplatin-based chemotherapy. This subgroup includes patients with poor renal function, who constitute a substantial proportion of bladder cancer patients. Paclitaxel and carboplatin appear well tolerated and show variable response rates in this disease in the region of 50% [9], although no regimen is established as standard therapy in this setting. Additionally, once patients with metastatic TCC relapse after first line chemotherapy, there is no standard

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treatment and recent data questions whether there is any benefit with chemotherapy here [10]. Therefore, this is a justified area for phase II clinical studies.

The study presented here investigates the use of 3 drugs, mitomycin, 5-fluorouracil (5-FU) and irinotecan (MFI) in patients with inoperable transitional cell cancer. The rationale for the combination was as follows. Mitomycin has an established role in this setting [11], while irinotecan has shown significant activity in laboratory models of bladder cancer [12]. Fluorouracil and folinic acid has single agent activity in cisplatin-refractory bladder cancer [13,14]. The combination of fluorouracil and irinotecan has been shown to be synergistic in various human xenografts [15]. The dose and schedule of irinotecan and mitomycin was based on the IPM regimen, which has been used other malignancies including renal cell and small cell lung cancer [16–18].

In view of the activity of these drugs both in vitro and clinically, this combination of drugs was chosen for use in patients not fit for cisplatin therapy or those relapsing after previous treatment with cisplatin.

2. Patients and methods

2.1. Eligibility

Between 2001 and 2004, patients with biopsy-proven metastatic/advanced (T4b-M1) TCC of the urinary tract were considered eligible ($n = 36$). These included 2 groups of patients: first, those with a calculated creatinine clearance less than 60 ml/min [19] who were not fit for cisplatin-based therapy ($n = 18$), and second, patients with relapsed disease after first line cisplatin-based chemotherapy ($n = 18$).

Patients were required to have an Eastern Co-operative Oncology Group (ECOG) performance status of 0–3, a white cell count (WBC) greater than 3.0×10^9/L, platelets greater than 100×10^9/L, and hemoglobin greater than 90 g/L (transfusions were permitted) prior to entry.

Patients were ineligible for recruitment to the study if they had previously received irinotecan, fluorouracil, or mitomycin. Previous intravesical mitomycin was, however, not a criterion for exclusion. Patients were also ineligible if they had previous non-transitional-cell malignancy, excluding completely excised non-melanomatous skin cancer, abnormal liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or bilirubin greater than 3 times the reference range).

The study was approved by the local research ethics committee, and all patients gave written informed consent prior to participation in the study.

2.2. Treatment

Mitomycin (6 mg/m^2) was given intravenously on day 1 of the schedule. 5-FU (500 mg/m^2) and folinic acid (30 mg bolus) were given, every 2 weeks, on days 1 and 15 as intravenous bolus doses. Irinotecan (100 mg/m^2) was given over 30 minutes on days 1 and 15. A maximum of 4 cycles was given.

2.3. Dose modifications

Treatment was delayed for a week if the blood count was low, with a total white cell count (WCC) of less than 3.0×10^9/l, neutrophils less than 1.0×10^9/l. A dose reduction of 50% of the mitomycin was made if, after 1 week, the platelet count was less than 75×10^9/l with neutrophils greater than 1.0×10^9/l. If the neutrophil count was less than 1.0×10^9/l, the irinotecan and 5-FU doses were also reduced by 20% on all subsequent cycles. All drugs, apart from folinic acid, were reduced by 20% in the event of an episode of neutropenic sepsis requiring intravenous antibiotics. Mitomycin was omitted on all subsequent occasions if the platelet count was less than 30×10^9/L. The dose of mitomycin was reduced by 50% on all subsequent cycles with a platelet count of $30–50 \times 10^9$/L.

2.4. Evaluation

All patients had a pretreatment full blood count, urea and electrolytes, liver function tests, and lactate dehydrogenase (LDH) prior to each cycle of therapy. All patients had a pretreatment CT scan of the abdomen and pelvis.

Table 1
Baseline characteristics

	All patients	1st line	2nd line
Number of patients	36	18	18
Median Age	69	72	63.5
Performance status			
0	4	3	1
1	10	6	4
2	10	4	6
3	10	4	6
Not documented	2	1	1
Serum creatinine (median)	138.5	145	107
Creatinine clearance (median) ml/min	47	36	58.5
Grade TCC			
G1	1	1	0
G2	8	2	6
G3	27	15	12
Symptoms			
Hematuria	17	11	6
Pain	23	12	11
Weight loss	6	2	4
Hydronephrosis	4	2	2
Malaise	6	1	5
Oedema	1	0	1
Sites of disease			
Only local (T4B)	3	3	0
Lymph nodes (+/– local)	16	7	9
Visceral metastasis	17	8	9