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Gemcitabine and cisplatin in locally advanced and/or metastatic bladder cancer

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Abstract

Although transitional cell carcinoma of the urothelium is chemosensitive, long-term disease-free survival is low. Accordingly, interest has focused on combining classically active agents like cisplatin with promising new drugs. Gemcitabine has evoked interest not only because of its intrinsic activity against this cancer, but also because of its effect of inhibiting repair of DNA that has been damaged by drugs like cisplatin. Four phase II studies have assessed the effect of a gemcitabine–cisplatin combination on advanced or metastatic bladder cancer. All the studies employed a gemcitabine dose of 1000 mg/m^2 given on days 1, 8 and 15, whereas the cisplatin dose and schedule varied, with total doses ranging from 70 to 105 mg/m^2. Overall response rates in these studies ranged from 42 to 66%, with complete responses from 15 to 28%. Toxicities, which were primarily haematological, were generally manageable. This promising two-drug combination has been compared with the standard MVAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin) in a randomised phase III trial and the results are eagerly anticipated.

Keywords: Advanced metastatic transitional cell carcinoma of the urothelium; M-VAC; Gemcitabine; Cisplatin

1. Introduction

Transitional cell carcinoma (TCC) of the urothelium is considered a chemosensitive tumour. None the less, chemotherapy confers only a modest survival benefit to these patients, and metastatic disease remains essentially incurable with only a small number of patients achieving long-term disease control.

A number of available drugs have significant single-agent activity against urothelial cancer, including cisplatin, methotrexate, doxorubicin, vinblastine, ifosfamide, and, more recently, gemcitabine and paclitaxel. Despite this activity, however, single-agent treatment generally achieves only partial responses (PRs) of short duration (median, 3–4 months).

Combination chemotherapy for advanced and metastatic TCC of the urothelium has been based most often on the most active single agents, cisplatin and methotrexate, which yield single-agent response rates of 30–35% [1]. As previously mentioned the MVAC combination (methotrexate, vinblastine, doxorubicin, cisplatin) is considered the standard for treatment of metastatic bladder cancer [2] with response rates of 40–72% [3–8] and median survival times of 12–13 months [9,10]. In a recent long-term study, however, only 3.7% of patients randomised to MVAC were alive and continuously disease free at 6 years [11]. The regimen is also associated with considerable treatment-related toxicity.

For these reasons, developing more effective and less toxic drug regimens to treat patients with TCC of the urothelium is vital. In this regard, gemcitabine has shown promising activity, with overall response rates of approximately 25% and complete response (CR) rates of approximately 10% [12–14]; toxicity, particularly myelosuppression, is mild.

2. Gemcitabine and cisplatin in patients with locally advanced or metastatic bladder cancer

The encouraging activity and tolerability of single-agent gemcitabine, coupled with its synergistic potential to inhibit DNA repair after a cell has been exposed to DNA-damaging agents like cisplatin [15], made it logical to study the combination of gemcitabine and cisplatin. Table 1 shows efficacy data from four phase II trials of this combination given to patients with locally advanced or metastatic TCC [16–19].

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Table 1
Responses to gemcitabine and cisplatin combination therapy in phase II studies of bladder cancer

Author [Ref.]	Dose and schedule		Prior chemotherapy	Evaluable patients (n)	CR/PR (n)	RR% (CR%)	Median survival (mo)
	Gemcitabine (mg/m^2)	Cisplatin (mg/m^2)					
von der Maase [16]	1000 days 1, 8, 15	35 days 1, 8, 15	None	38	7/9	42% (18%)	12.5
Kaufman [17]	1000 days 1, 8, 15	100/75[a] day 1	Adjuvant >6 months before study entry	47	13/18	66% (28%)	NR
Moore [18]	1000 days 1, 8, 15	70 day 2	Adjuvant >12 months before study entry	28	6/10	57% (21%)	13.2
Mancarella [19]	1000 days 1, 8, 15	70 day 2	Adjuvant >12 months before study entry	54	8/18	48% (15%)	9

CR, complete response; PR, partial response; RR, overall response rate; NR, not reported.
[a] First 13 patients received 100 mg/m^2 and 34 patients received 75 mg/m^2.

In the first phase II study, a European study, our group administered gemcitabine 1000 mg/m^2 plus cisplatin 35 mg/m^2 on days 1, 8 and 15 every 28 days to patients with locally advanced or metastatic TCC [16]. Patients could not have received prior systemic chemotherapy. The median age of the 42 patients enrolled in the study was 64 years (range: 48–74 years), the female:male ratio was 11:31, and the median Karnofsky performance status score was 90 (range: 70–100). Sites of metastases included lung, liver and bone in 4, 12 and 9 patients, respectively. Of the 38 patients evaluable for response, 7 (18%) had CRs and 9 (24%) partial response (PR), for an overall response rate of 42%. 7 of 9 patients with lymph node metastases responded. Responses were also observed in patients with pulmonary (1 patient), hepatic (2 patients) and bone (3 patients) metastases. The median duration of overall response was 13.5 months (range: 8–48+ months), and the median survival was 12.5 months (95% confidence interval (CI), 8.1–18.7 months). At the time of analysis, 4 patients were still alive with responses continuing after 32–48 months. The most important toxicity was myelosuppression, with grade 3–4 neutropenia in 58% and grade 3–4 thrombocytopenia in 78% of patients. No severe bleeding episodes, grade 4 infections or toxic deaths occurred. Non-haematological toxicities were primarily nausea and/or vomiting, with grade 3 toxicity in 22% and grade 4 toxicity in 7% of patients. Toxicities were generally manageable, but dose reductions and omissions were necessary in 54% of gemcitabine cycles and in 37% of cisplatin cycles because of myelosuppression and, to a lesser extent, decreasing renal function. The dose intensities of gemcitabine and cisplatin were 74% and 80%, respectively.

Kaufman and colleagues [17] reported preliminary results of a US multicentre, phase II trial of gemcitabine and cisplatin in patients with metastatic or locally recurrent TCC of the urothelium. Patients were initially treated with gemcitabine 1000 mg/m^2 given on days 1, 8 and 15 and with cisplatin 100 mg/m^2 given on day 1. Doses were repeated on a 28-day cycle for a maximum of six cycles. Due to severe myelosuppression, with most patients experiencing grade 3–4 neutropenia or thrombocytopenia, the cisplatin dose was reduced to 75 mg/m^2 after the first 13 patients had been treated; thus, 34 patients received the lower dose. After this dose reduction, haematological toxicity diminished significantly. Patients could not have received prior chemotherapy for metastatic disease, but those whose adjuvant or neoadjuvant chemotherapy had been completed at least 6 months before study enrolment were eligible to participate. All of the 47 patients who entered the study were evaluable for response. Their median age was 61 years (range: 37–80 years), the female/male ratio was 10/37, and the median Karnofsky performance status score was 90 (range: 70–100). Metastatic sites included lung, liver and bone in 7, 2 and 1 patients, respectively. 13 patients (28%) had CRs and 18 (38%) PRs, for an overall response rate of 66%. Responses occurred at all disease sites, including lymph node (predominant site), urinary bladder, lung, liver and bone. After a mean follow-up of 9.3 months, 83% of the patients were still alive. After the cisplatin dose had been reduced to 75 mg/m^2, grade 3–4 neutropenia and thrombocytopenia occurred in 49 and 45% of patients, respectively.

Moore and colleagues [18] initiated a Canadian phase II study involving patients with TCC of the bladder in which gemcitabine 1000 mg/m^2 was given on days 1, 8 and 15 and cisplatin 70 mg/m^2 was given on day 2, with courses repeated every 4 weeks. Patients could not have received prior chemotherapy for metastatic cancer, but adjuvant or neoadjuvant chemotherapy was allowed so long as it had been completed at least 12 months before enrolment. A total of 31 patients entered the study. Their median age was 69 years and their median Eastern Cooperative Oncology Group performance status was 1 (range: 0–2). The most common metastatic sites included lymph nodes, bladder, liver and bone in 21, 13, 8

and 9 patients, respectively. Several patients had more than one metastatic site. In 28 evaluable patients, the overall response rate was 57%, including 6 CRs (21%) and 10 PRs (36%). The median durations of CR and PR were 9.6 and 7.5 months, respectively. Median survival was 13.2 months with 4 patients still in remission at the time of this analysis. The primarily haematological toxicity was reasonable; 39% of patients had grade 3 neutropenia, and 55% had grade 3 thrombocytopenia. 2 patients had febrile neutropenia. All patients required a gemcitabine dose reduction at some point during therapy, primarily because of thrombocytopenia and/or neutropenia; these dose reductions occurred primarily on day 15.

Using the same regimen of gemcitabine and cisplatin, Mancarella and colleagues [19] evaluated 54 patients who had not received previous chemotherapy for metastatic disease. The median age of the patients was 67 years. Previous adjuvant cisplatin-based chemotherapy was allowed so long as it had concluded more than 12 months before entry into the study. All patients were evaluated for response and toxicity (intent-to-treat). Responses were observed in 26 patients (48%) with 8 patients (15%) attaining a CR. The median time to progression was 26 weeks, and the median survival time was 9 months. Of the 32 patients with disease-related symptoms (haematuria, pain, weight loss), 16 (50%) improved. Grade 3–4 leucopenia was observed in 21 patients (39%) and grade 4 neutropenia in 6 patients (11%). 28 patients (52%) needed gemcitabine doses reduced or omitted on day 15 because of neutropenia or thrombocytopenia. No other relevant side-effects were observed.

3. Conclusion

Gemcitabine and cisplatin represent an encouraging two-drug combination in patients with locally advanced or metastatic TCC of the urothelium. Toxicities are generally manageable although the weekly cisplatin schedule resulted in a high degree of grade 3–4 neutropenia and thrombocytopenia. Thus, cisplatin doses of 75 or 70 mg/m^2 given every 28 days as opposed to the weekly schedule appears to be the optimal cisplatin schedule for the combination.

The four phase II studies of gemcitabine plus cisplatin described herein have reported promising overall response rates of 42–66% and CR rates of 15–28%. These high, durable response rates have been attained without compromising tolerability, and the CR rates compare favourably with the rates (10–20%) observed with other cisplatin-based regimens [2]. Responses were also seen in patients with bone and visceral metastases. It could be of benefit to use a 21-day schedule to reduce the need for gemcitabine dose reductions on day 15 when using the 28-day schedule.

Only a randomised phase III trial can clarify whether this new two-drug regimen is superior or equivalent to other effective regimens. Since MVAC is considered the standard in the treatment of TCC of the urothelium, it follows that the classic MVAC regimen should be challenged in this setting. Therefore, a multinational, multicentre, randomised, phase III study comparing the two-drug combination of gemcitabine and cisplatin with MVAC in patients with locally advanced or metastatic TCC of the urothelium was initiated late in 1996. This study applied a weekly gemcitabine schedule of 1000 mg/m^2 on days 1, 8 and 15 and cisplatin 70 mg/m^2 administered on day 2, i.e. the same cisplatin dose and schedule as used in the comparative MVAC regimen. The planned recruitment of 400 patients was reached at the end of October 1998, and results are eagerly anticipated.

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