# *A 3-week gemcitabine-cisplatin regimen for metastatic urothelial cancer*

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***Objective:*** *To assess the efficacy and tolerability of a 3-week outpatient schedule of intravenous gemcitabine and cisplatin in patients with locally advanced unresectable or metastatic transitional cell carcinoma of the urothelial tract (TCC).*

***Patients and methods:*** *A two-stage phase II trial enrolled TCC patients with Karnofsky performance status ≥ 60, measurable disease, and adequate organ function. Prior adjunctive chemotherapy was allowed provided it had been completed at least 1 year prior to study entry. Treatment consisted of gemcitabine 1250 mg/m$^2$ iv days 1 and 8 plus cisplatin 70 mg/m$^2$ day 1 iv repeated every 21 days. The primary outcome was the objective response rate.*

***Results:*** *Thirty patients were enrolled at six Canadian centres. Three complete and 10 partial responses were observed in 29 eligible patients (overall response rate 45% [95%CI, 27-63%]). Three patients had stable disease and 13 had progressive disease. The relative dose-intensities of gemcitabine and cisplatin were 81% and 88%, respectively. Toxicity was primarily hematological, and 60% of patients experienced at least one episode of grade 3 or 4 toxicity. One patient died of neutropenic sepsis and two died of vascular events while on treatment.*

***Conclusions:*** *The efficacy and tolerability of this schedule are similar to that reported with the standard 4-week schedule of gemcitabine-cisplatin. In the absence of a large randomized trial, the similarity of these results supports the use of this 3-week program in typical TCC patients treated in both community and academic cancer clinic settings.*

**Key Words:** bladder neoplasms, drug therapy, gemcitabine, cisplatin

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## Introduction

Chemotherapy for metastatic transitional cell cancer (TCC) has evolved over the last two decades to the extent that responses are now common and complete clinical remissions occur in a significant minority of patients. Despite these advances cure remains elusive and the toxicity of chemotherapy remains notable. A combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) improved survival compared to single agent cisplatin and for many was established as a standard of therapy for TCC.[1] M-VAC

has considerable toxicity, though this can be mitigated with the use of growth factor support.[2]

Gemcitabine is a fluorinated cytosine analogue with significant single agent activity in both chemotherapy naïve and pre-treated TCC patients.[3-5] This observation led to the development of gemcitabine-cisplatin regimens that showed considerable activity, prompting a randomized trial versus M-VAC.[6-8] The results of this trial demonstrated similar survival irrespective of the treatment received by 405 randomized patients, but with less clinically significant toxicity and need for hospitalization in the gemcitabine-cisplatin arm.[9] The gemcitabine-cisplatin regimen studied administered gemcitabine on days 1, 8 and 15 and cisplatin on day 2, with cycles repeated every 28 days. Most treatment omissions for myelosuppression occurred on day 15, suggesting this as a logical rest day in a modified schedule. In non-small cell lung cancer, more recent trials have utilized these two drugs on a 21-day cycle with enhancement of the planned dose intensity of both agents over the course of therapy.[10,11] The administration of cisplatin on day 1 is also widely used in non-small cell lung cancer, and may be more convenient for patients.[12] We performed a phase II trial to determine the efficacy and safety of a 3-week outpatient regimen as first-line chemotherapy in TCC.

## Patients and methods

Patients were considered eligible for this Canadian multicentre phase II study if they had locally advanced unresectable or metastatic transitional cell carcinoma of the urothelial tract not amenable to curative surgical or radiotherapy. Patients could have received prior radiotherapy provided it had been completed at least 4 weeks prior to study entry, or prior systemic therapy either as surgical adjunct or radiation sensitizer provided it had been completed at least 1 year prior to study entry. Eligible patients had a Karnofsky performance status of at least 60, a life expectancy of at least 12 weeks, no major comorbid conditions, bidimensionally measurable disease, and adequate haematological, renal and hepatic function. The study was conducted in accordance with the Helsinki Declaration, was approved by local research ethics boards, and all patients provided written informed consent.

Gemcitabine was administered intravenously at a dose of 1250 mg/m$^2$ days 1 and 8 with cisplatin administered intravenously at a dose of 70 mg/m$^2$ day 1 following the gemcitabine infusion either as inpatient or outpatient. Therapy could be continued to a maximum of six cycles for stable disease or up to six cycles beyond documented objective response. No dose escalation was permitted and dose reductions were based on pre-specified toxicity criteria as measured by the WHO toxicity scale.[13] Response was assessed according to bidimensional WHO criteria. In brief, complete response was characterized by the disappearance of all known disease determined by two observations not less than 3 weeks apart without evidence of new lesions and stability of non-measurable lesions. Partial response was defined as a 50% or greater decrease in the sum of the products of bidimensionally measurable lesions observed at least 3 weeks apart. Clinically measurable lesions were assessed at each cycle, and CT scans were repeated every 6 weeks while on therapy.

The primary outcome of this study was the objective response rate. Secondary outcomes included response duration, toxicity, and overall survival. A two-stage phase II design was employed with assessment of the response rate after the initial 16 patients had been enrolled. If five or more responses were identified in this cohort the study would proceed to a projected sample size of 38 patients. This was estimated sufficient to determine if the response rate was 40% or greater with a power of 0.80 and a type-1 error of 0.05, with a probability of 80% of stopping the study in the first stage if the response rate is 20% or less. The relative dose-intensities (RDIs) of gemcitabine and cisplatin were calculated by dividing the received cumulative dose of each drug by the full dose the patient should have received during the treatment period.[14] All confidence intervals for estimated parameters were constructed with a significance level = 0.05, that is a 95% confidence interval. For response rates, exact limits were computed using the F-distribution.[15] Time to survival, time to progressive disease and time to response were analyzed using the Kaplan-Meier[16] estimated survival curves.

## Results

### *Patients*

Thirty patients were enrolled between December 1999 and December 2001 at six Canadian sites, including two community cancer clinics Table 1. One patient was ineligible due to lack of bidimensionally measurable disease, and was withdrawn after three cycles of therapy; however, this patient was included in the toxicity analyses. The trial closed July 2002 due to slow accrual. This was attributed to widespread adoption of gemcitabine-cisplatin therapy for the treatment of TCC following publication of the favorable results of a randomized trial.[9] The median age of patients was

TABLE 1. **Patient characteristics (n=30)**

| | Characteristic | Number of patients |
|---|---|---|
| Median age (range) | 63 years (39-92) | 30 |
| | < 70 | 22 |
| | ≥ 70 | 8 |
| Gender | Female | 4 |
| | Male | 26 |
| Performance status (Karnofsky) | ≥ 70 | 28 |
| | < 70 | 2 |
| Primary site | Bladder | 26 |
| | Renal pelvis | 3 |
| | Urethra | 1 |
| Pathology | Transitional cell carcinoma | 30 |
| Extent of disease at entry | Locally advanced | 4 |
| | Metastatic | 26 |
| Sites of disease (n=29) | Lung | 6 |
| | Lymph nodes | 17 |
| | Liver | 4 |
| | Bladder/urothelium | 11 |
| | Pelvis | 9 |
| | Bone | 3 |
| Number of sites of disease | 0 | 1 |
| | 1 | 2 |
| | 2 | 10 |
| | 3 or more | 17 |
| Visceral metastases (lung, liver, or bone) | | 12 |
| Elevated serum alkaline phosphatase | | 5 |
| Adverse prognostic factors (n=29) | 0 | 13 |
| | 1 | 8 |
| | 2 | 5 |
| | 3 | 3 |

63 years (range, 39 to 92 years), and 26 patients were male. Twenty-six patients had cancers that arose from the bladder and 18 had prior cystectomy. Karnofsky performance status less than 80; the presence of visceral metastases in lung, liver, and/or bone; elevation of alkaline phosphatase; and age 70 or greater have been identified as independent adverse prognostic factors in large randomized trials of TCC.[1,9] Sixteen patients had at least one adverse prognostic factor, and three patients had three adverse features. Metastatic disease was present in 26 of 29 patients, and was most commonly described in lymph nodes (17 patients), lung (6 patients) and liver (4 patients).

### *Treatment delivery*

A total of 138 and a median of 5 cycles of therapy (range, 1-8) were administered to the 30 patients. Thirteen patients completed six or more cycles of therapy. Of the remaining 17 patients, 10 discontinued treatment after less than six cycles due to disease progression. Three died while receiving study therapy due to neutropenic sepsis, pulmonary embolism, and stroke; respectively. Two patients discontinued study therapy due to toxicity (protracted neutropenia, and grade 3 hearing loss), one patient withdrew from the trial after cycle 1, and the ineligible patient was withdrawn after cycle 3. Fifty-two gemcitabine doses were modified (18.8%); 43 doses were reduced and 9 were omitted. Twenty-five of the reductions and all of the omissions were on day 8. The RDI of gemcitabine was 81% [95% CI, 77-86%], equivalent to 676 mg/m$^2$/week. Thirteen cisplatin doses (9.4%) were reduced and none were omitted. The RDI of cisplatin was 88% [95% CI, 84-92%], equivalent to 20.6 mg/m$^2$/week.

### *Toxicity*

The most common and severe toxicities were myelosuppression and nausea and vomiting Table 2. Eighteen patients (60%) experienced a grade 3 or higher

TABLE 2. **Grade 3 or greater toxicities (worst by patient) (n=30)**

| Toxicity | Grade 3 | 4 | 5 | Total (%) |
|---|---|---|---|---|
| Granulocytes | 6 | 7 | 1 | 14 (47) |
| Platelets | 4 | 2 | | 6 (20) |
| Hemoglobin | 8 | | | 8 (27) |
| Alkaline phosphatase | | 1 | | 1 (3) |
| Blood urea nitrogen | 1 | | | 1 (3) |
| Nausea/vomiting | 5 | | | 5 (17) |
| Pulmonary embolus | | | 1 | 1 (3) |
| Stroke | | | 1 | 1 (3) |
| State of consciousness | 1 | | | 1 (3) |
| Any (%) | 16 (53) | 8 (27) | 3 (10) | 18 (60) |

toxicity on at least one occasion during treatment. Four patients experienced an episode of febrile neutropenia. One of these patients died due to neutropenic sepsis following febrile neutropenia occurring during cycle 2. One patient died of a nonhemorrhagic stroke and one of pulmonary embolus.

### *Response and survival*

Twenty-nine eligible patients were potentially evaluable for response; one of these patients withdrew after cycle 1 and was not reassessed. There were three complete responses and 10 partial responses observed. The objective response rate considering all 29 eligible patients was 45% [95% CI, 27-63%]. Excluding the patient not re-evaluated, the response rate was 46% [95% CI, 28-65%]. The median duration of response was 8.8 months [range, 0.7-28.6 months]. Of the 12 patients with visceral metastases, one complete response (hepatic metastases) and four partial responses in patients with lung (2 patients), bone, and liver plus bone metastases were observed. Twenty-three patients have died, 19 as a result of their cancer. The median survival time for the 29 eligible patients was 9.1 months (95% CI, 6.0-12.0 months). Progressive disease or death occurred in 23 of the 29 eligible patients at a median time of 7.1 months (95% CI, 3.0-12.7 months). Six patients remain alive with evidence of disease 1.3 to 10.2 months after study enrolment.

## Discussion

Therapy for TCC has evolved over the last decade, and most patients are now offered systemic chemotherapy with a reasonable expectation of benefit and evidence that treatment can prolong survival.[1] Although the tolerability of chemotherapy has improved, the search for more effective, tolerable, and convenient regimens continues. The main objective of this study was to pragmatically ascertain the efficacy and tolerability of a truncated and more dose-intense schedule of gemcitabine-cisplatin. The treatment schedule studied differed from standard 4-week gemcitabine-cisplatin in several ways. A 3-week instead of a 4-week schedule was used, and the dose of cisplatin was identical, but was administered on day 1 following the first dose of gemcitabine. By eliminating a visit to the chemotherapy unit, cisplatin given day 1 is potentially more efficient and convenient, and overall time of treatment could be reduced by 6 weeks if six cycles of therapy were planned. While only two doses of gemcitabine were given each cycle, the doses scheduled were 25% higher than the standard 4-week regimen, and the planned dose intensity was 11% higher for gemcitabine and 33% higher for cisplatin. The RDI of gemcitabine in our study (676 mg/m$^2$/week) was 13% higher than the RDI achieved with the 4-week schedule.[6] The RDI of cisplatin (20.6 mg/m$^2$/week) was 18% higher than the planned dose intensity of cisplatin given every 4 weeks.

Changes to the scheduling of gemcitabine and cisplatin should raise concerns about possible schedule-dependent antagonism or toxicity; however, there are few published data suggesting deleterious effects of either gemcitabine given prior to cisplatin on day 1 or 3-week scheduling. Data from preclinical studies have shown either additive or synergistic antitumour activity with gemcitabine given prior to or simultaneously with cisplatin.[17-19] Increasing the time between gemcitabine prior to cisplatin increased toxicity in two xenograft studies.[18,20] Three clinical analyses of the effects of gemcitabine-cisplatin scheduling have been published.[21-23] Cassidy et al[21] reviewed data from 1441 patients receiving gemcitabine-cisplatin treatment in either phase II of phase III trials, and reported that rates of grade 3 or 4 thrombocytopenia were reduced with 3-week schedules compared to 4-week schedules in patients receiving cisplatin $\leq$ 75 mg/m$^2$ (n=617) (30.2% and 48.8%, respectively, p=0.001). No such difference was seen in patients receiving cisplatin 100 mg/m$^2$ (n=824). Abratt et al[22] examined results from six phase II studies of 4-week schedules of gemcitabine-cisplatin in non-small cell lung cancer, and concluded that less severe myelosuppression was observed when cisplatin 100 mg/m$^2$ was given on day 15 of a 4-week schedule, as opposed to day 1, 2, or with weekly fractionated administration. Shepherd et al[23] pooled the results of these trials to examine effects on response rate and overall survival. A multivariable model suggested that day 2 or 15 cisplatin 100 mg/m$^2$ administration was superior to day 1 or weekly fractionated administration for both response and overall survival. However, given the higher cisplatin dose studied, the limited number of patients (n=279), and the lack of justification for the trial groupings analyzed, this analysis should be viewed as hypothesis generating. Notwithstanding these observations, treatment of patients with non-small cell lung cancer continues with administration of both drugs on day 1 of each cycle in both clinical trials and practice.[12]

Our study is obviously limited in its ability to conclude the 3-week program is equivalent to the standard 4-week program due to its sample size, patient characteristics, and the absence of a comparator arm. Including more patients might improve the precision of the estimate of the response rate, but would change its magnitude little. With intent-to-treat analyses, the overall response was 45% and commensurate with the

phase II response rate of 52% reported by Moore et al[7] and phase III response rate of 44.5% reported by von der Maase et al.[9] We cannot exclude a clinically significant higher or lower response rate with certainty; however, the relatively small differences between these response rates are consistent with similar antitumor activity, and are likely explained by differences in patient selection between trials. Similarly, we cannot exclude with certainty somewhat higher rates of toxicity, and this might be expected with the higher dose intensity of treatment delivered.

This being said, this 3-week treatment regimen was tolerable and had a manageable and expected toxicity profile. One patient died of neutropenic sepsis, and two patients died as a result of significant vascular events. While the latter must be considered possibly related to the treatment regimen in light of a report of increased rates of vascular events in TCC patients treated with cisplatin-based polychemotherapy,[24] there were no observations of deaths due to vascular toxicity from either gemcitabine-cisplatin or M-VAC in a large randomized trial comparing these regimens.[9] Czaykowski et al[24] noted in their report that many of the venous thrombotic events were associated with bulky pelvic disease. We do not have data to confirm this finding in our two patients. In the absence of local factors contributing to the vascular events in our patients it is possible the more intense 3-week regimen may be a contributory factor. It is notable that one-third of the patients were enrolled outside university-affiliated centres, and the demographic characteristics of our cohort of patients appear representative of TCC patients typically seen in the clinic rather than in phase II clinical trials. Our data suggest that 3- and 4-week gemcitabine-cisplatin are comparable in efficacy and safety. The higher dose intensity delivered and shorter treatment time required raise a logical interest in use of this regimen in the adjuvant setting. □

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