Gemcitabine and cisplatin after radical cystectomy for bladder cancer in an adjuvant setting: feasibility study from the Genito-Urinary Group of the French Federation of Cancer Centers

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The impact of adjuvant chemotherapy in locally advanced bladder cancer is still not fully established. Between January 2000 and November 2001, 30 patients entered the trial to receive four cycles of a combination of gemcitabine 1250 mg/m^2 on day 1 and day 8 and cisplatin 70 mg/m^2 on day 1, repeated every 3 weeks. Histologic diagnoses included pT2–pT3–pT4 tumors and/or pN1–pN2. Combination treatment with gemcitabine and cisplatin was considered feasible if 70% of the patients received a relative dose intensity of each drug of more than 90%. Twenty-seven patients received four cycles of combination treatment. The relative dose intensity of cisplatine and gemcitabine was 96 and 88%, respectively. No toxic death occurred. We conclude that giving four cycles of the gemcitabine–cisplatin regimen in the adjuvant setting after cystectomy is feasible with a manageable toxicity and a high relative dose intensity. Whether this approach may increase survival is currently assessed in a randomized trial. ***Anti-Cancer Drugs*** **17:705–708 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Invasive bladder cancer accounts for 20–30% of all newly diagnosed bladder cancers. Bladder cancer is the second most common cancer of the genitourinary system. The standard treatment for muscle-invasive bladder cancer is radical cystectomy and pelvic lymphadenectomy. In all, 20–30 and 35% of patients with pelvic lymph node (pN1 or pN2) or extravesical (pT3 or pT4a) involvement are long-term survivors, respectively. During the late 1980s, different groups have performed phase III studies testing adjuvant chemotherapy in this patient population with the aim of increasing survival [1–4]. These trials, however, were impaired by significant weaknesses including, mainly, a limited number of patients and a poor dose intensity of the chemotherapy arms. Therefore, the benefit of adjuvant chemotherapy is still uncertain and debated. One potential way to improve these results would be to identify an active regimen with a better dose intensity. We present the results of a feasibility study of a combination of gemcitabine and cisplatin in the adjuvant setting after radical cystectomy and pelvic lymphadenectomy. The efficacy of this association in advanced bladder cancer has previously been demonstrated in a phase III study [5].

Patients and methods

Patients

Between January 2000 and November 2001, 30 patients with transitional cell muscle-invasive bladder carcinoma (pT2 grade 3, pT3 or pT4) with or without pelvic lymph node involvement (pN1 or pN2) were enrolled in seven institutions. Histological confirmation of muscle invasion by tumor was a prerequisite for inclusion in the study. All patients had radical cystectomy with pelvic lymph node dissection. None had distant metastatic disease detectable by whole-body computed tomography scan or chest X-ray and ultrasonography of the pelvis and abdomen. Patients had a performance status of grade 0–2. They were expected to receive chemotherapy within 3 months after surgery. Inclusion criteria were renal function calculated according to the Cockroft and Gault formula greater than 50 ml/min, absolute neutrophil count more than 2 g/l, platelet count more than 150 g/l, hemoglobin rate more than 9 g/dl, bilirubin $\leq 1.25 \times$ upper limit of

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normal, aminotransferases $\leq 3\times$ upper limit of normal and absence of moderate or severe heart failure. Patients had to be fit to receive four cycles of chemotherapy, not previously treated by chemotherapy and free from any other previous cancer (except *in situ* cervix cancer and basocellular skin tumor). The study was approved by the ethics committees of participating institutions. We obtained written informed consent from all patients.

Objectives of the study

The primary endpoint of the study was the feasibility of gemcitabine and cisplatin combination chemotherapy in the adjuvant setting. Secondary endpoints were toxicities, time to progression and overall survival.

Treatment

Chemotherapy was started within 3 months following cystectomy. It consisted of gemcitabine 1250 mg/m^2 administered as a 30- to 60-min intravenous infusion on days 1 and 8, and cisplatin 70 mg/m^2 given as a 60-min intravenous infusion on day 1. Cisplatin was infused 4 h after gemcitabine, together with hydration and standard anti-emetics. This schedule was repeated every 21 days over four cycles.

Statistical analysis

Thirty patients received the association of gemcitabine and cisplatin.

Combination treatment with gemcitabine and cisplatin was considered feasible if 70% of the patients received a relative dose intensity of each drug of more than 90% [21 of 30 patients with a confidence interval of 95% (51–85%)]. Median follow-up, time to progression and overall survival were calculated and estimated by the Kaplan–Meier method. Patients who were still alive were censored at the date of the last follow-up visit. The analysis was performed in December 2004.

Toxicities

Toxicities were evaluated according to the World Health Organization classifications.

Dose adjustment

Treatment was not administered on day 8 if platelets and absolute neutrophil counts were under 75 and 1 g/l, respectively. Cisplatin was not administered on day 1 when renal function calculated according to the Cockroft and Gault formula was between 50 and 30 ml/min, and stopped under 30 ml/min. Treatment was not administered for all grade 3 toxicities and was stopped for all grade 4 toxicities.

Results

Initial patient characteristics are shown in Table 1. Histological patterns of radical cystectomy were not centrally reviewed. One hundred and fifteen cycles of chemotherapy with gemcitabine and cisplatin were administered on day 1. One patient received one cycle, two patients received three cycles and the other 27 (90%) received four cycles. Ninety cycles (78%) of gemcitabine were administered on day 8. Cycles with dose reduction and those that were delayed are presented in Table 2; this consisted of 85 cycles (with the exclusion of the first cycle). Thirty-four of the 85 cycles were delayed and/or reduced. Chemotherapy was delayed in four cycles because of toxicity in 14 cycles and the patient's personal problems. All patients had at least one undercurrent event (grade 1 +) during treatment. Grade 3/4 neutropenia was observed in 22 patients (73.4%), but only three (10%) cases of febrile neutropenia occurred. Grade 3/4 thrombocytopenia was observed in seven (23.4%) patients; platelet transfusions were performed 7 times. Grade 3/4 anemia necessitating transfusion with packed erythrocytes was observed in two patients. Other grade 3 toxicities included acute cardiac failure in one patient, vomiting in eight cycles and asthenia in three cycles. One patient had grade 1 renal toxicity. The details of all toxicities are presented in Table 3.

Gemcitabine and cisplatin relative dose intensities are summarized in Table 2.

Table 1 Patient characteristics

	Number of patients (n=30)	
	n	Percentage
Sex		
male	22	73
female	8	27
Age (years)		
Median	58	40–75
<60	17	57
≥ 60	13	43
WHO performance status		
0	17	57
1	12	40
2	1	3
pT category		
2	8	27
3	12	40
4	10	33
pN status		
x	2	6
0	6	20
1	11	37
2	11	37
Histological grade		
2	2	7
3	27	93
unknown	1	–
Time cystectomy/inclusion (weeks)	8.6	3.6–13.1
Hemoglobin		
grade 0	27	90.0
grade 1	3	10.0
ANC		
grade 0	30	100.0
Platelets		
grade 0	30	100.0
Calculated glomerular filtration rate (ml/min)	58.5 (34.0:96.0)	

WHO, World Health Organization; ANC, absolute neutrophil count.

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Table 2 Treatment administration

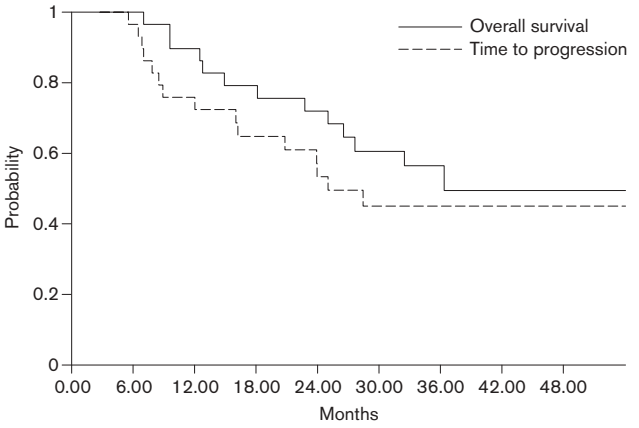
Patient	Number of patients ($n=30$)	Median (min:max)
Treatment duration (days)	30	85.5 (21.0:106.0)
Cumulative dose (mg/m^2)		
gemcitabine	30	8823.3 (2463.8:10 047.5)
cisplatin	30	279.3 (68.8:298.8)
Dose intensity (mg/m^2/week)		
gemcitabine	30	729.4 (402.4:842.7)
cisplatin	30	22.3 (18.3:24.3)
Relative dose intensity		
gemcitabine	30	0.88 (0.48:1.01)
cisplatin	30	0.96 (0.79:1.04)
Relative dose intensity (%)		
gemcitabine		
<90	16	53.3
≥ 90	14	46.7
cisplatin		
<90	8	26.7
≥ 90	22	73.3

Table 3 Hematological and other toxicities

	Number of patients ($n=30$) (%)	
	Grade 1–2	Grade 3–4
ANC	8 (26.6%)	22 (73.4%)
Platelets	12 (30%)	7 (23.4%)
Hemoglobin	23 (76.7%)	2 (6.7%)
Nausea/vomiting	15 (50%)	8 (26.7%)
Diarrhea	5 (16.6%)	–
Mucosal toxicity	4 (13.4%)	–
Renal toxicity	3 (10%)	–
Cardiac toxicity	–	1 (3.3%)
Hepatic toxicity	1 (3.3%)	–
Peripheral neuropathy	5 (16.7%)	–
Ototoxicity	3 (10%)	–
Fatigue	19 (63.4%)	3 (10%)
Alopecia	11 (36.6%)	–
Other	–	1 (3.3%)

ANC, absolute neutrophil count.

Fig. 1



Overall survival and time to progression curves.

The median time of follow-up was 35.3 months. The median time to progression and overall survival were 25 and 36.4 months, respectively. Twelve patients had a relapse during follow-up and 17 were alive at the time of analysis. The overall survival and time to progression calculated by Kaplan–Meier are 89.7 and 75.9% at 1 year, 72 and 53.4% at 2 years, and 56.5 and 45% at 3 years, respectively (Fig. 1).

Discussion

The treatment of locally advanced and metastatic bladder cancer has been based on cisplatin since the early 1980s. Two randomized trials have led to the acceptance of a combination with methotrexate, vinblastine and doxorubicin (MVAC) as the standard therapy since the early 1990s [6,7]. In 2000, a randomized trial by von der Maase *et al.* [5] compared the association of gemcitabine and cisplatin with MVAC; the study showed no superiority of one regimen over the other with regard to overall survival, but evidenced a lower toxicity with gemcitabine and cisplatin. This regimen thus became a standard of treatment for metastatic urothelial tumors. The role of adjuvant chemotherapy in patients with advanced bladder cancer or loco-regional lymph node involvement has not yet been well demonstrated. Four randomized trials with different chemotherapy regimens have been performed [1–4]. The number of patients in these studies is very small and no advantage in overall survival can be defined. It has, however, been indicated that patients with lymph node involvement might possibly benefit from adjuvant chemotherapy. Results of adjuvant chemotherapy in invasive bladder cancer meta-analysis were recently published. The results were in favor of adjuvant chemotherapy, although this study was clearly underpowered to make definitive conclusions [8].

We present the first results of an association of gemcitabine and cisplatin in the adjuvant setting. To improve the dose intensity of cisplatin, we have chosen a schedule of administration of gemcitabine and cisplatin different from that in the international study. In the international study, patients received cisplatin 70 mg/m^2 on day 2, and gemcitabine 1000 mg/m^2 on days 1, 8 and 15, although many day 15 doses were not given [5]. In our study, patients received gemcitabine at a dose of 1250 mg/m^2 on days 1 and 8, and cisplatin 70 mg/m^2 on day 1. We observed that the relative dose intensities of cisplatin and gemcitabine were 96 and 88%, respectively. In the international study, 63% of gemcitabine and cisplatin cycles were administered without dose adjustment, and dose intensity was 80% for gemcitabine and 102% for cisplatin. In the other studies testing adjuvant chemotherapy, the feasibility of chemotherapy was poor: 65% of the patients received the chemotherapy regimen (cisplatin) in the study by Studer *et al.* [4], 75% in the study by Skinner *et al.* [3], and 47% received all four cycles of the association of cisplatin, cyclophosphamide and adriamycin, 60% all four cycles of the association of carboplatin and paclitaxel in the study by Bamias *et al.*

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[9]. The feasibility of chemotherapy after radical cystectomy is classically low for different reasons: patient age, insufficient renal function, type of surgery and toxicity of the treatment.

Regarding toxicity, the incidence of febrile neutropenia (10%) was moderate, and 23.4 and 73.4% had grade 3/4 thrombopenia and neutropenia, respectively. These toxicities are lower than those described with the MVAC regimen [5].

The median time to relapse in our study was 25 months, a time interval similar to that of other studies using adjuvant chemotherapy: 13.6 and 16.2 months in the studies reported by Stockle *et al.* [2] and Freiha *et al.* [1], respectively. The overall survival at 3 years was 56.5%, but the median time of follow-up was only 35.3 months. The average 5-year survival rate of patients with lymph node involvement was 25% in different series (0–36%) [2–4]. It is difficult to compare these results.

In conclusion, the association of gemcitabine and cisplatin is feasible in the adjuvant setting after cystectomy and the relative dose intensity is higher than what was previously reported with other active regimens such as MVAC [5]. An international randomized study comparing adjuvant chemotherapy (MVAC or gemcitabine and cisplatin) and late chemotherapy (gemcitabine and cisplatin) in patients who had a relapse is ongoing. We hope that this international study can shed some light on the indication of adjuvant chemotherapy in advanced bladder cancer and we strongly recommend that investigators who see these patients include them in this trial.

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