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ORIGINAL ARTICLE

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Gemcitabine plus carboplatin; and gemcitabine, docetaxel, and carboplatin combined chemotherapy regimens in patients with metastatic urothelial carcinoma previously treated with a platinum-based regimen: preliminary report

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Abstract
Background. The aim of this study was to evaluate the efficacy and safety of two combined chemotherapy regimens in the treatment of previously treated metastatic urothelial carcinoma: gemcitabine plus carboplatin (GC), and gemcitabine, docetaxel, and carboplatin (GDC).
Methods. Sixteen patients with metastatic urothelial cancer, previously treated with a platinum-based regimen, were studied. GC (gemcitabine 750 mg/m^2, on days 1, 8, and 15; carboplatin 200 mg/m^2, on day 2) was administered every 28 days to 15 patients. GDC (gemcitabine 750 mg/m^2, on days 1 and 8; docetaxel 50 mg/m^2, on day 1; carboplatin 200 mg/m^2 on day 1) was administered every 21 days to 9 patients. Eight of the 9 GDC-treated patients had earlier been treated with GC and had become refractory.
Results. With the GC therapy, 7 of the 15 treated patients (47%; 95% confidence interval, 21%–73%) showed an objective response, with 3 achieving a clinical complete response (CR) and 4 a partial response (PR). With the GDC therapy, 6 of the 9 treated patients (67%; 95% confidence interval, 29%–92%) showed an objective response, with 1 achieving CR and 5, PR. Five of the 8 (63%) GC-refractory patients responded to GDC therapy. The median duration of response was 4 months (range, 2–10+ months) on GC therapy, and 3 months (range, 3–5 months) on GDC therapy. Toxicities associated with GC were less than those with GDC.
Conclusion. GC was effective for refractory metastatic urothelial cancer, and GDC was effective for GC-refractory cancer.

Key words Gemcitabine · Docetaxel · Metastatic urothelial cancer

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Introduction

Gemcitabine, a cell-cycle-specific pyrimidine nucleoside analog, is converted within the cell to triphosphate metabolites. The incorporation of gemcitabine triphosphate into actively replicating DNA and masked-chain termination results in the inhibition of DNA synthesis.[1,2]

Gemcitabine exhibits significant activity in metastatic transitional cell cancer (TCC), with minimal toxicity, but it has little effect on increasing patient survival. Trials of gemcitabine in combination with other active agents have thus been suggested.[3] Paclitaxel was originally a natural product derived from the bark of the North American yew tree, *Taxus brevifola*. Clinical studies using paclitaxel commenced in the mid-1980s. French researchers produced an extract of the European yew, *Taxus baccata*, and modified it with a chemically synthesized side chain. Docetaxel emerged as a result of these efforts and entered clinical trials in 1990.[4] Docetaxel is capable of inducing bcl2 phosphorylation and apoptotic cell death at 100-fold lower concentrations than paclitaxel.[5]

At present, the combination of cisplatin, methotrexate, doxorubicin, and vinblastine (M-VAC)[6] is most widely used for advanced TCC and has shown overall response rates of 40%–72% in phase II studies and 35%–45% in phase III studies, with a median survival of approximately 12 months. These modest results and unsuccessful attempts to increase

Table 1. Characteristics of patients receiving GC and/or GDC chemotherapy

Patient no.	Age (years)	Sex	Disease site	Previous chemotherapy	Response to GC	Response duration (months)	Response to GDC	Response duration (months)	Survival after GC and/or GDC chemotherapy (months)
1	52	M	LN, lung	MEC, M-VAC	PD				3
2	72	M	LN	M-VAC, ITP	CR	5			8
3	68	M	Bone	MEC, ITP	NC				24+
4	56	M	Bone	MEC, M-VAC	PD				8+
5	68	M	LN	MEC, ITP	CR	5			8+
6	71	M	LN	MEC, ITP	CR	10+			11+
7	61	M	LN, Lung, liver	ITP	PD				3
8	46	M	Lung	MEC	PD		PR	3	12+
9	68	M	Lung	MEC	PR	3	CR	3	6
10	73	M	Liver	M-VAC	PR	8	PR	5	15
11	66	M	Lung	MEC	PR	2	PR	3	4+
12	68	M	LN	MEC, ITP	PD		PD		10+
13	51	M	LN, lung, liver	MEC, ITP	PD		PD		12
14	69	M	LN, lung, liver	M-VAC	PD		PD		5+
15	55	M	Liver	M-VAC	PR	3	PR	3	10+
16	73	M	LN, liver	MEC			PR	5	6+

M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; MEC, methotrexate, epirubicin, cisplatin; ITP, ifosfamide, paclitaxel, cisplatin; GC, gemcitabine, carboplatin; GDC, gemcitabine, docetaxel, carboplatin; LN, lymph node; PD, progressive disease; CR, complete response; PR, partial response; NC, no change

the efficacy with dose-intensive M-VAC schedules have prompted the identification of new agents active against TCC, such as the taxanes and gemcitabine. The overall response rates for two-drug regimens consisting of cisplatin-paclitaxel, carboplatin-paclitaxel, and cisplatin-gemcitabine range from 63% to 72%, 14% to 65% and 42% to 66%, respectively. The overall response rates for platinum-paclitaxel-gemcitabine three-drug regimens range from 58% to 80%.[7]

We administered two-drug and three-drug combinations of these new drugs as a pilot study in patients with metastatic urothelial carcinoma whose tumors were refractory to or had shown no response to platinum-based regimens.

Patients and methods

From August 1998 to May 2003, we treated 16 patients with metastatic urothelial cancer who had previously received one or more platinum-based regimens. The previous chemotherapies had been MEC[8] (methotrexate, epirubicin, cisplatin) in 11 patients, M-VAC[6] in 6, and ITP[9] (ifosfamide, paclitaxel, cisplatin) in 7 patients. Informed consent was obtained from all patients, and this clinical study was done with the Institutional Review Board's approval.

The patients were all men, with a mean age of 64 years (range, 46 to 73 years). Thirteen patients had bladder cancer and 3 had pelvic or ureteral cancer. The pathological diagnoses of the primary tumors were all grade II to III TCC. Two patients had already undergone radical cystectomy and 2 patients, nephroureterectomy. Metastases were limited to the lymph nodes in 4 patients; to the lymph node and lung in 1 patient; to the lymph nodes, lung, and bone in 1 patient; and to the lymph nodes, lung, and liver in 3 patients. Metastases were restricted to only the lung in 3 patients, to only the bone in 2, and to only the liver in 2 (Table 1).

Treatment

The treatment schedule for the combination of gemcitabine and carboplatin (GC) was gemcitabine 750 mg/m^2 over 30 to 60 min on days 1, 8, and 15; and carboplatin 200 mg/m^2 on day 2. Cycles were repeated every 28 days.[10] The treatment schedule for the comination of gemcitabine, docetaxel, and carboplatin (GDC) was gemcitabine 750 mg/m^2 on days 1 and 8, docetaxel 50 mg/m^2 on day 1, and carboplatin 200 mg/m^2 on day 1. Cycles were repeated every 21 days.[11,12] These treatments were carried out for a maximum of eight cycles of GC and six cycles of GDC in responding patients or patients with stable disease, but they were discontinued in the presence of disease progression. A detailed medical interview, clinical examination, and laboratory studies were obtained before each drug administration. Dose adjustment was based on assessment of the hematological and nonhematological toxicities. In particular, only 75% of the gemcitabine dose was administered when granulocytes measured 1.0–1.4 $\times$ 10^9/l and/or platelets were 75–99.9 $\times$ 10^9/l. If granulocytes were 0.5–0.9 $\times$ 10^9/l and/or platelets were 50–74.9 $\times$ 10^9/l, 50% of the full dose was administered. If the cell counts fell below the lower level of either range, further treatment was delayed until recovery.

GC was administered to 15 patients and GDC to 9 patients. Eight of the 9 GDC-treated patients had previously been treated with GC and had become refractory (Table 1). The median time from discontinuation of GC to the start of GDC in these 8 patients was 1 month. The median number and range of cycles of GC therapy were 3 and 2 to 8. The median number and range of cycles of GDC therapy were 3 and 1 to 6.

Evaluation of response and toxicity

All patients who completed at least one therapy cycle (three injections of gemcitabine and tumor reassessment after a 1-week interval) were analyzed for chemotherapeutic efficacy. All enrolled patients were analyzed for toxicity and survival and were reviewed every month to assess efficacy and toxicity. After discontinuation of treatment, patients were evaluated every month to assess the survival and disease-free status. The evaluation of the tumor response was based on the standard WHO criteria for measurable disease.[13]

For the evaluations of the tumor response and survival, the following definitions were used: time to response, the time from first injection to first objective response; time to progression, the time from first injection to the date of evidence of progression; time to treatment failure, the time from first injection to date of withdrawal from the study for any reason (progression, toxicity, refusal); duration of partial response (PR), the time from first evidence of PR to the time of disease progression; duration of complete response (CR), the time from first evidence of CR to the time of disease progression; and survival, the time from first injection to death.

Kaplan-Meier analysis was used for analysis of the survival and time to progression, and the 95% confidence interval (CI) was also calculated.

Results

Response

Fifteen patients received at least two courses of GC and 9 patients received at least one course of GDC, so only these patients were evaluated for response and toxicity. With the GC therapy, 7 of the 15 patients (47%; 95% CI, 21%–73%) showed an objective response, with 3 achieving a CR and 4, a PR. The time to response in all responders was within 2 months. With the GDC therapy, 6 of the 9 treated patients (67%; 95% CI, 29%–92%) showed an objective response, with 1 achieving CR and 5, PR. Five of the 6 responders were refractory to GC therapy, and in all 6 patients the time to response was 1 month. The median duration of response was 4 months (range, 2–10+ months) with GC and 3 months (range, 3–5 months) with GDC (Table 1). The median times to progression with the GC and GDC therapies were 4.5 months and 4 months, respectively. The median survival for all patients was 8 months.

All three CRs in patients on GC therapy occurred in the lymph nodes, while the one CR in the patient on GDC therapy occurred in the lung. The four PRs in patients on GC therapy occurred in the liver and lungs, while the PRs in patients on GDC therapy occurred in lungs in two patients and the liver in three patients.

Three of the six patients with liver metastasis achieved a PR. Patient 10 (patient number in Table 1) had multiple liver metastases, jaundice, and total bilirubin of 10 mg/dl when he was referred to our hospital. GC therapy was performed by hepatic arterial infusion by inserting an arterial infusion catheter into the femoral artery through a port set in the femoral subcutaneous area. PR was obtained within two cycles. After eight cycles; however, new liver metastasis appeared, and so we switched to GDC therapy. The new liver metastasis decreased, and PR was obtained again and continued for 5 months. His bilirubin level dropped to the normal range, and tumor markers[14] (carcinaembryonic antigen [CEA], carbohydrate [CA] 19-9, and CA125) also decreased to almost normal ranges. However, with these chemotherapies (eight cycles of GC and five cycles of GDC) computed tomography (CT) showed atrophy of liver without elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or alkaline phosphatase (ALP), but endoscopy showed esophageal varices. We diagnosed the occurrence of liver cirrhosis caused by fibrotic change of massive metastatic liver tumor necrosis after chemotherapy. Accordingly, we terminated the chemotherapy, and the patient died 2 months later, with multiple liver metastases and ascites. In patient 15, the liver lesion responded to GC and GDC therapies and PRs were obtained and continued for 3 and 3 months, respectively. In patient 16, a 1.5-cm liver metastasis had appeared during the previous MEC therapy for pelvic lymph node metastases. The liver lesion responded to GDC therapy, and PR was obtained and continued for 5 months.

In patient 9, lung metastasis occurred during GC therapy but responded to GDC therapy; CR was obtained, but the duration was only 3 months. GDC therapy resulted in a PR of 3 months' duration in patients 8 and 11 with lung metastasis which had become refractory to GC therapy.

Toxicity

The treatments were generally well tolerated (Tables 2, 3). Grade 3 pancytopenia was observed in two patients treated with GC and in seven patients treated with GDC. The incidence of infection related to neutropenia was 11% (1/9) in patients on GDC therapy, with no WHO grade 3–4 infections. There were no cases of WHO grade 3–4 biochemical toxicity of AST/ALT, ALP, or bilirubin, and no transient elevation of AST, ALT, or ALP. No patients had WHO grade 3–4 elevation of the serum creatinine level or blood

Table 2. Toxicity of GC according to WHO toxicity scale(n = 15)

Toxicity	Grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Neutropenia	0	0	7	7
Anemia	0	0	7	7
Thrombocytopenia	0	0	13	0
Neuropathy	0	0	0	0
Myalgia	0	0	0	0
Alopecia	0	0	0	0
Diarrhea	13	0	0	0

GC, gemcitabine, carboplatin; WHO, World Health Organization

Table 3. Toxicity of GDC according to WHO toxicity scale ($n = 9$)

Toxicity	Grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Neutropenia	0	0	22	55
Anemia	0	0	55	22
Thrombocytopenia	0	0	33	33
Neuropathy	0	0	0	0
Myalgia	0	0	0	0
Alopecia	0	50	50	0
Diarrhea	22	11	0	0

GDC, gemcitabine, docetaxel, carboplatin; WHO, World Health Organization

urea nitrogen (BUN). With regard to symptomatic toxicity, nausea and vomiting were generally modest. Alopecia occurred in all GDC-treated patients.

Discussion

Transitional cell carcinoma (TCC) of the urothelium is a chemosensitive tumor, as demonstrated by its overall response rate of 35%–70% with the M-VAC drug combination.[6] The toxicity of this regimen, however, is significant, and the median survival of all treated patients does not greatly exceed 12 months.[15,16] These results have prompted a search for new active agents which could be incorporated into more effective and less toxic regimens.

Gemcitabine has been studied as a single agent for the treatment of metastatic bladder cancer,[3,17] and, based on its mechanism of action, it was thought to have potential for synergism with cisplatin. This synergism was later confirmed.[18]

Liver metastases generally do not respond well to M-VAC. On the other hand, liver metastases have a chance to respond to gemcitabine, as noted by Pollera et al.[17] They reported that three of seven patients with liver metastasis responded well to gemcitabine. Stadler et al.[3] also stated that three of nine patients with liver metastasis achieved a CR on gemcitabine monotherapy. One of our patients with multiple liver metastases survived for 15 months. When he was referred to our hospital, his total bilirubin was 10 mg/dl and jaundice was seen. Arterial infusion chemotherapy with GC was dramatically effective, and his bilirubin value dropped after two courses of GC. Almost the same effect was observed in patient 16. In another patient, a 1.5-cm liver metastasis had been found during MEC therapy for pelvic lymph node metastasis, but GDC therapy was effective, and a PR was obtained.

GC provides a survival advantage similar to that seen with M-VAC, while having a better safety profile and tolerability. [19] This better risk ratio should lead to a change in the standard of care for patients with metastatic TCC, with chemotherapy changed from M-VAC to GC.

Our results showed that some tumors which had become refractory to GC were still sensitive to GDC. Among our eight patients refractory to GC treatment, five (63%) responded to GDC. The responding organ was the lung in two patients and the liver in three patients. Therefore, we think GC is suitable as a first-line chemotherapy, and GDC is useable as a second-line chemotherapy. However, the durations of the response to GC and GDC therapies were short, so a new combination chemotherapy showing a longer response is desired. The metastatic urothelial tumors which became refractory to GC had a chance to respond to GC plus docetaxel (GDC chemotherapy). To our knowledge, this is the first published report showing that GDC is effective for GC-refractory metastatic urothelial tumors. It remains unclear whether, in order to prolong the chemotherapy effect, GC should be used as first-line chemotherapy, with GDC as second-line therapy; or whether GDC should be used as first-line chemotherapy. Accordingly, a double-blind randomized study of two arms, GC to GDC and GDC, is now in progress.

All of our patients had previously received cisplatin-based chemotherapy and radiotherapy. GC showed mild toxicity (patients experienced little WHO grade 3 toxicity), which was easily manageable. GC is usually well tolerated and is suitable for outpatient use. Neither unexpected nor cumulative toxic effects were found. Furthermore, the absence of significant renal and cardiac toxicities makes this promising combination especially attractive for urothelial cancer, allowing GC to be used in patients who may not be able to tolerate more toxic chemotherapeutic regimens.

We showed that metastatic urothelial tumors refractory to GC therapy still responded to GDC therapy. However, GDC therapy had the disadvantage of a short duration of response. Accordingly, another combination chemotherapy of gemcitabine with an epidermal growth factor receptor inhibitor is now being investigated.[20]

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