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ORIGINAL ARTICLE

Phase I study of gemcitabine-cisplatin versus pemetrexed-cisplatin for patients with advanced or metastatic bladder cancer

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Summary

Purpose: *The present study aimed to compare the chemotherapeutic regimens of gemcitabine plus cisplatin (GC) vs pemetrexed plus cisplatin (PC) in bladder cancer (BC) with vascular invasion and/or distant metastasis.*

Methods: *From January 2010 to January 2017, 53 patients with advanced or metastatic BC were included and randomly divided into two groups. Patients in the GC group were administered 1,000 mg/m² gemcitabine on day 1 and 15 and 70 mg/m² cisplatin on day 1 as an IV infusion. Patients in the PC group were administered 500 mg/m² pemetrexed on day 1 and 15 and 70 mg/m² cisplatin on day 1 as an IV infusion. The two regimens were repeated every 28 days. Patients were treated for about 4–6 cycles until the occurrence of severe toxicity or patient refusal.*

Results: *The median overall survival (OS) and the median progression-free survival (PFS) in the GC group were significantly higher than that in the PC group (OS: p=0.033 and PFS: p=0.039, respectively). Besides, the response rates and disease control were obviously higher in the GC group (68% and 86%, respectively) compared to the PC group (44% and 56%, respectively), although without statistical significance. Regarding toxicity, higher rates of neutropenia and nausea in the PC group were noted, while thrombocytopenia was more frequent in the GC group.*

Conclusions: *The gemcitabine plus cisplatin combination was more effective and well tolerated in patients with advanced or metastatic BC compared to the pemetrexed plus cisplatin regimen.*

Key words: *bladder cancer, chemotherapy, cisplatin, gemcitabine, pemetrexed*

Introduction

Bladder cancer (BC) is estimated to be the sixth most common cancer and the seventh most common cause of cancer-related mortality in the US [1]. Approximately 25% of incident bladder cancers are muscle-invasive and approximately 25% of them will harbor metastatic disease at the time of cystectomy [2,3]. Unfortunately, metastatic bladder cancer remains, in the majority of cases, an incurable disease. Urothelial carcinoma (UC) is the most common histologic subtype of BC and accounts for nearly 90% of all the cases [4]. UC is a well-known chemosensitive disease. Polychemotherapy leads to overall response rates (ORR) between 50 and 70% [5], but the cure rate of BC is far from satisfactory due to resistance to some chemotherapeutics. Thus, for most patients with BC, more effective anticancer chemotherapy is in urgent need.

Despite improvements in recent surveillance programs, lots of BC patients are diagnosed at advanced stage, with distant metastasis or vascular invasion, for which cisplatin-based combination chemotherapy is currently considered as a standard treatment for metastatic and non-resectable

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BC [6]. The combination of methotrexate, vinblastine, doxorubicin and cisplatin, known as MVAC, is associated with an objective response rate of 39-65% and has long been regarded as the gold standard for first-line treatment of metastatic BC [7]. In recent years, the combination of gemcitabine and cisplatin (GC) has demonstrated equivalent efficacy as well as lower toxicity, and has become largely the regimen of choice, despite a slight trend toward greater efficacy with MVAC therapy [8]. However, complete responses with either regimen are rare and progression to cancer-related death is inevitable for most patients with metastatic disease. Given the inability to cure metastatic BC with current chemotherapeutic regimens, more effective regimens are under study to treat locally advanced or regional metastatic disease.

Pemetrexed is a potent inhibitor of thymidylate synthase [9] and some other folate-dependent enzymes [10]. Pemetrexed as a single agent has achieved favourable responses with tolerated toxicities in the treatment of advanced UC [11]. In recent years, the combination of pemetrexed plus cisplatin (PC) has been attempted in a large spectrum of malignant diseases, showing superior efficacy and benefit compared to the gemcitabine plus cisplatin regimen or cisplatin alone in patient with non-small-cell lung cancer [12] or malignant pleural mesothelioma [13]. Concerning there is no other proven effective chemotherapy available for advanced BC patients, additional treatments are needed. Thus, it is interesting to explore if pemetrexed plus cisplatin is as effective as gemcitabine plus cisplatin for the treatment of inoperable locally advanced or metastatic BC.

The present trial was conducted as a randomized controlled phase I study to investigate the efficacy and feasibility of pemetrexed plus cisplatin for treating advanced or metastatic bladder cancer compared to gemcitabine plus cisplatin. Our aim was to determine if pemetrexed plus cisplatin is a beneficial alternative regimen to gemcitabine plus cisplatin.

Methods

Patient selection

In this trial selected were 53 patients diagnosed with locally advanced or metastatic BC and divided randomly into two groups. One group was treated with gemcitabine plus cisplatin, while the other with pemetrexed plus cisplatin at the Jiaxing First Hospital from January 2010 to January 2017. Patients eligible for the study were those with histologically confirmed muscle-invasive carcinoma of the bladder and with locally advanced, locally relapsed or metastatic disease. Detailed investigations were carried out before chemotherapy for all the included patients, including abdominal CT, chest CT and brain CT. Each patient provided informed consent before the study entry.

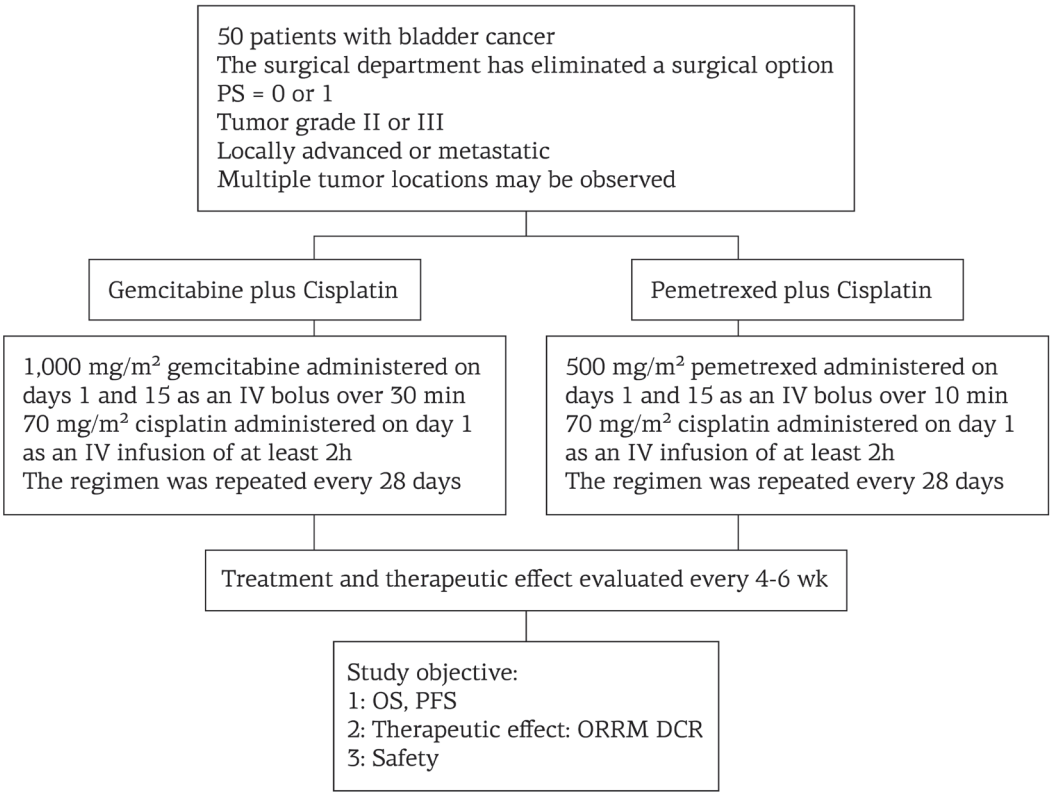

Figure 1. Flow chart of the treatment scheme.

Inclusion/exclusion criteria

The inclusion criteria in this study were as follows: age ≤75 years, ECOG performance status (PS) ≤1, tumour grade II or III, adequate renal function (glomerular filtration rate ≥440 ml min^{-1}), adequate haematological function (Hb ≥10.0 g dl^{-1}, platelets ≥100×10^9 l^{-1}, neutrophils ≥2.0×10^9 l^{-1}), and adequate liver function (serum bilirubin within normal limits, ALP<1.5 times the upper limit of normal (ULN), or up to 2.5 times the ULN with liver metastases and ALP up to 2.5 times with bone metastases. The exclusion criteria were as follows: patients treated with any other prior anti-tumor drugs and development of some serious complications, including active infection, severe renal and respiratory failure, severe heart disease, and poorly controlled diabetes mellitus/hypertension.

This study was approved by the ethics committee of Jiaxing First Hospital.

Treatment schedule

All included BC patients were randomly divided into two groups to receive gemcitabine plus cisplatin (GC) or pemetrexed plus cisplatin (PC) chemotherapy. As shown in Figure 1, patients in the GC group were administered 1,000 mg/m^2 gemcitabine on day 1 and 15 as an IV bolus over 30 min and 70 mg/m^2 cisplatin on day 1 as an IV infusion over 2 hrs. Patients in the PC group were administered 500 mg/m^2 pemetrexed on days 1 and 15 as an IV bolus over 10 min and 70 mg/m^2 cisplatin on day 1 as an IV infusion over 2 hrs. The two regimens were repeated every 28 days. Patients were treated for about 4–6 cycles until the occurrence of unacceptable toxicity or patient refusal. Dose modification was allowed when toxicity was out of tolerance. Patients were put under follow-up until death or study termination.

Evaluation of toxicity and response

During chemotherapy, serum biochemistry, complete blood counts and abdominal CT were performed once a week. Responses to the regimens were assessed according to the Response Evaluation Criteria in Solid Tumor (RECIST) [14]. For all the BC patients, the toxicity of the two chemotherapy regimens was assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 [15].

Table 1. Baseline patient characteristics

Characteristics	*Gemcitabine plus Cisplatin n=28 n (%)*	*Pemetrexed plus Cisplatin n=25 n (%)*	*p value*
Gender			0.805
Male	21 (75.0)	18 (72.0)	
Female	7 (25.0)	7 (28.0)	
Age (years)			0.086
Median	60	64	
Range	41-71	42-75	
ECOG performance status			0.776
0	18 (64.3)	17 (68.0)	
1	10 (35.7)	8 (32.0)	
Tumour grade			0.340
II	1 (3.6)	0 (0)	
III	27 (96.4)	25 (100)	
Disease status			0.563
Locally advanced disease	8 (28.6)	9 (36.0)	
Metastatic disease	20 (71.4)	16 (64.0)	
Sites of disease[a]			0.829
Bladder	11 (39.3)	10 (40.0)	
Lymph nodes	15 (53.6)	15 (60.0)	
Lung	5 (17.9)	6 (24.0)	
Liver	6 (21.4)	3 (12.0)	
Bone	4 (14.3)	2 (8.0)	
Prior treatments			0.830
Chemotherapy	0 (0)	0 (0)	
Intravesical therapy	3 (10.7)	2 (8.0)	
Radiotherapy	4 (14.3)	5 (20.0)	
Surgery	21 (75.0)	18 (72.0)	

[a]Multiple locations may be observed

Statistics

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. All quantitative data were expressed as mean ± standard deviation. Comparison between groups was done using one-way ANOVA test followed by *Post Hoc* Test (least significant difference). Percents (%) were used to express the enumeration data and x^2 test was used for data analysis. PFS was defined as the time interval from the chemotherapy initiation to disease progression or death. OS was defined as the time interval from treatment initiation to the death of patients. The data for the surviving patients were censored on the day they were found alive at the last follow-up. Patients who were progression-free or alive were carefully censored until the last follow-up. Rates of PFS and OS were calculated with Kaplan-Meier method and log-rank test was used to find differences between groups. P values<0.05 were considered statistically significant.

Results

Characteristics of patients

Baseline characteristics of selected patients are shown in Table 1. No statistically significant differences were found between the two groups concerning age, gender, ECOG PS, tumour grade, pathological stage, tumor location and prior treatments.

Toxicity

The adverse events observed in all 53 patients are listed in Table 2. Regarding grade 3 or higher toxicities of chemotherapy, higher rates of neutropenia and nausea were noted in the PC group (neutropenia, p=0.021; nausea, p=0.044), while grade 3 or more severe thrombocytopenia was noted in the GC group (p=0.033). There were no significant differences concerning other toxicities between the two chemotherapy regimens. Also, no treatment-associated death occurred in either group.

The median number of chemotherapy cycles was 3.5 (range 1-6) in the GC group and 3.3 (range 1-6) in the PC group. There were no significant differences in the numbers of chemotherapy cycles between the two treated groups (p=0.531).

Response to treatment

Among the 28 patients in the GC group, 5, 3, 19 and 1 showed stable disease (SD), progressive disease (PD), complete response (CR)/ partial response (PR) and not evaluated (NE), respectively. As shown in Table 3, the response rate of the GC treatment was 68%, and the rate of disease control was up to 86%. Meanwhile, among the 25 patients in the PC-treated group, 9, 3, 11 and 2 patients showed a PD, SD, CR/PR and NE, respectively. The response rate of the PC treatment was 44% and the disease control rate was 56%. The rates of response and disease control were obviously higher in the GC group compared to the PC group, yet not reaching statistically significant difference (response rate, p=0.121; disease control rate, p=0.108).

Survival

As shown in Figures 2 and 3, the median OS and PFS were 15.7 months (range 2.2-33.5) and 9.4 months (range 0.6-26.2) in the GC group. On the other hand, the median OS and PFS were 10.6 months (range 1.4-29.2) and 5.1 months (range 0.6-22.2) in the PC group. The data showed that the median OS and the median PFS in the GC group were both significantly higher compared with the PC treated (OS: p=0.033; PFS: p=0.039).

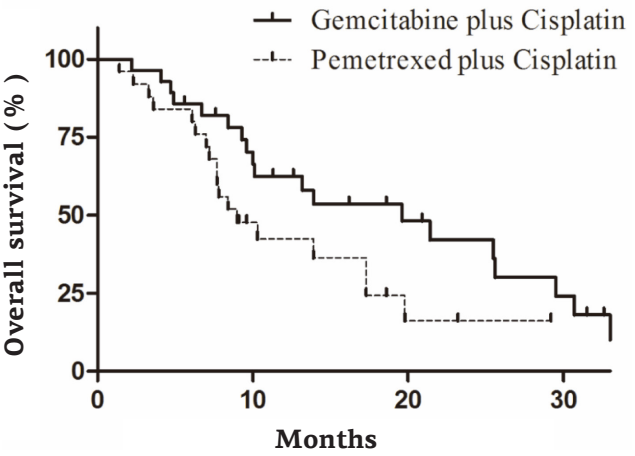

Figure 2. Kaplan-Meier overall survival of the patients treated with gemcitabine plus cisplatin and pemetrexed plus cisplatin (p=0.033).

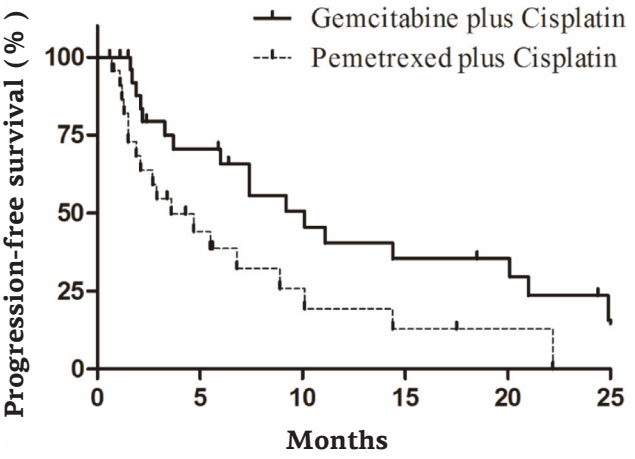

Figure 3. Kaplan-Meier progression-free survival of the patients treated with gemcitabine plus cisplatin and pemetrexed plus cisplatin (p=0.039).

Table 2. Toxicities in the two combination therapies: gemcitabine plus cisplatin (GP; n=28) and pemetrexed plus cisplatin (PC; n=25)

Toxicities		*Gr1*	*Gr2*	*Gr3*	*Gr4*	*≥Gr3 (p value)* %		*All (p value)* %	
Neutropenia	*GC*	5	4	1	1	7	0.021	39	0.072
	PC	4	4	5	3	32		64	
Anaemia	*GC*	4	3	2	0	7	0.906	32	0.991
	PC	3	3	2	0	8		32	
Thrombocytopenia	*GC*	3	1	4	3	25	0.033	39	0.060
	PC	2	1	1	0	4		16	
AST/ALT elevation	*GC*	2	1	1	0	4	0.935	14	0.580
	PC	3	1	1	0	4		20	
Creatinine elevation	*GC*	3	2	1	0	4	0.486	21	0.823
	PC	3	1	1	1	8		24	
Nausea	*GC*	12	3	1	1	7	0.043	61	0.024
	PC	9	6	5	2	28		88	
Anorexia	*GC*	9	6	1	0	4	0.486	57	0.833
	PC	6	7	2	0	8		60	
Constipation	*GC*	6	5	0	0	0	0.285	39	0.728
	PC	7	3	1	0	4		44	
Diarrhea	*GC*	5	4	1	0	4	0.935	36	0.138
	PC	6	7	1	0	4		56	
Mucositis	*GC*	8	4	1	0	4	0.486	46	0.284
	PC	2	4	2	0	8		32	
Fatigue	*GC*	17	6	2	0	7	0.546	89	0.735
	PC	13	7	3	0	12		92	
Myalgia	*GC*	2	3	1	0	4	0.340	21	0.823
	PC	4	2	0	0	0		24	
Oedema	*GC*	6	3	1	0	4	0.486	36	0.983
	PC	5	2	1	1	8		36	
Infection	*GC*	4	2	2	1	11	0.756	32	0.991
	PC	3	3	2	0	8		32	
TEEs	*GC*	3	1	1	1	7	0.621	21	0.823
	PC	3	2	1	0	4		24	
Pulmonary embolism	*GC*	2	4	1	0	4	0.935	25	0.572
	PC	4	3	1	0	4		32	
DVT	*GC*	3	2	1	0	4	0.340	21	0.614
	PC	3	1	0	0	0		16	
MCI	*GC*	3	1	0	0	0	0.285	14	0.580
	PC	2	2	1	0	4		20	
Anuria	*GC*	1	4	2	1	11	0.735	29	0.963
	PC	2	3	1	1	8		28	

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TEE: thromboembolic event, DVT: deep vein thrombosis, MCI: myocardial infarction

Table 3. Tumor response to PC and GC regimens

Response	*Gemcitabine plus Cisplatin, n=28*		*Pemetrexed plus Cisplatin, n=25*	
CR/PR	19	68	11	44
SD	5	18	3	12
PD	3	11	9	36
NE	1	4	2	8
Response rate (%)	68 *		44 *	
Disease control rate (%)	86**		56 **	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluated. P value *0.121 by x^2 test and **0.108 by Fisher's exact test

Discussion

In this study GC and PC were compared concerning their toxicity, response to treatment and survival. To our knowledge this is the first randomized controlled trial to compare the effect of these combinations in advanced BC with distant metastasis or vascular invasion. Median survival of patients in the GC group was 15.7 months and one-year survival 53.6%. Both median OS and PFS in the GC group were significantly higher compared with the PC group. In addition, response and disease control rates were also higher in the GC group (68% and 86%, respectively) compared to PC group (44% and 56%, respectively), although without statistical significance. Regarding the grade 3 or higher toxicities of chemotherapy, higher rates of neutropenia and nausea were noticed in the PC group. On the other hand, we found frequent occurrence of grade 3 or more thrombocytopenia in the GC group.

In the past several years, cancer chemoprevention concerning the use of natural or synthetic agents to inhibit, retard or reverse tumorigenesis, has received lots of attention [16,17]. Demonstrating the underlying mechanisms involved in the anticancer activity will provide valuable evidence for the development of newer and hopefully more efficacious anticancer drugs. Treatment of metastatic BC has not undergone any major changes in the past 30 years [18]. The median OS of patients has not exceeded 15 months, and cisplatin-based chemotherapy regimens remain the mainstay of treatment [19]. GC is a gold-standard first-line systemic chemotherapy for advanced UC. However, it may cause severe adverse effects such as renal toxicity, gastrointestinal toxicity, and neurotoxicity [20]. Cisplatin binds to serum proteins easily, resulting in a smaller portion of the injected platinum excreted into the urine [21]. In our study, we found frequent occurrence of grade 3 or more severe thrombocytopenia in the GC group. Maybe the chemical properties of cisplatin are responsible for the severe adverse effects observed in the present trial. Some studies have reported that the GC regimen achieved 45-60% overall response rates (ORRs), a median OS of 14-15 months, and a median PFS of 7-8 months [22,23], which were comparable with the results of the present study.

Pemetrexed is a novel antifolate used in the treatment of various tumors [24,25]. Sweeney et al. [26] have reported that pemetrexed as a single agent could provide a 27.7% ORR and a median OS of 9.6 months in patients with advanced or metastatic BC. In another trial, biweekly administration of 400 mg m^{-2} pemetrexed plus 50 mg m^{-2} cisplatin was found achieving 39.5% ORR, a median OS of 10.5 months and a median PFS of 6.7 months. This biweekly combination also showed tolerable toxicities with the most frequent grade 3-4 toxicities being asthenia (5%) and neutropenia (13%) [27]. Patients treated with PC showed 44% ORR and higher rates of nausea and neutropenia in our study. These results were supported by the previously reported randomized trials [26,27].

The results of our study showed that both the median OS and the median PFS in the GC treated group patients were significantly higher than in the PC treated group. Besides, the response and the disease control rates were also higher in the GC treated group compared to the PC group, although without statistical significance. In addition, toxicities of the two chemotherapy regimens were comparable and tolerated by most of the patients. Therefore, GC remained more effective and well tolerated in most of the patients with advanced or metastatic BC compared with the PC regimen. More randomized studies comparing PC are warranted. The GC regimen was proved a better alternative to some other standard regimens. However, the clear mechanisms underlying the pemetrexed action and its utility for the treatment of BC need to be further investigated.

Conclusions

In summary, compared to the PC regimen, GC was more effective and less toxic in patients with advanced or metastatic BC.

Acknowledgements

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Conflict of interests

The authors declare no conflict of interests.

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