Serum C-reactive protein level is a significant prognostic indicator in patients with advanced urothelial cancer treated with gemcitabine-cisplatin or carboplatin – preliminary results

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KEY WORDS

biomarker ◗ CRP ◗ peripheral blood value ◗ survival ◗ chemotherapy

ABSTRACT

Introduction. This study determines prognostic factors in patients with advanced urothelial cancer (UC) treated with gemcitabine-cisplatin or carboplatin (GC).

Material and methods. The clinical records of 30 patients with advanced UC treated with GC were retrospectively reviewed. Twenty-six patients (86.7%) had previously undergone other chemotherapies. Hematological parameters such as: neutrophil, lymphocyte and platelet counts; hemoglobin, C-reactive protein (CRP), and albumin levels; pain score; primary tumor site; tumor grade; type of platinum anti-cancer drug; and performance status before treatment were evaluated. Survival rates were calculated using the Kaplan-Meier method and analyzed using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards model.

Results. The median cancer-specific survival (CSS) was 12.5 months. The overall response rate (ORR) was 30.0%. The survival rates of patients with low serum albumin (<3.5 g/dL; P = 0.008), low hemoglobin (<10.1 mg/dL; P = 0.025), high CRP (>1.0 mg/dL; *P* = 0.001), and a positive pain score (P = 0.002) were significantly worse than those with better blood values and pain scores. Multivariate analysis revealed serum CRP level as an independent prognostic indicator with a hazard ratio of 4.608 (95% confidence interval (CI) of 1.763-12.047; P = 0.002).

Conclusions. Pretreatment serum CRP levels could be an accurate biomarker of the survival of patients with advanced UC before GC therapy. Although this is a preliminary study with a small sample size, these results seem to be very useful in clinical practice and our findings should be confirmed in a larger group of patients.

INTRODUCTION

Despite recent developments in anti-cancer drugs, advanced urothelial cancer (UC) remains incurable with a median survival of 13-15 months [1]. The methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimen originally reported by Sternberg is now in common use worldwide [2]. However, the MVAC regimen is associated with substantial toxicity and a toxic death rate of 3-4% [3, 4]. Therefore, we usually use methotrexate, epirubicin, and cisplatin (MEC) to treat patients with advanced UC. This regimen has less adverse drug reactions and a randomized trial has demonstrated that it is as effective as the MVAC regimen [5]. A multinational phase III trial of 405 patients compared MVAC with a gemcitabine-cisplatin (GC) regimen in 2000 [1]. The results showed that GC provides a similar survival advantage to MVAC with a better safety profile and tolerability. The substitution of cisplatin with carboplatin seems to be a promising alternative for patients with advanced UC who are often elderly, and have impaired renal function because of repeated chemotherapy and radical nephroureterectomy [6-10]. Carboplatin is an analog of cisplatin with a different side-effect profile [11]. The dose-limiting toxicity of carboplatin is myelosuppression, but at standard doses it is less emetogenic and does not cause nephrotoxicity, ototoxicity, or neurotoxicity. Several phase II clinical studies have found equivalent therapeutic results between gemcitabine-carboplatin and GC [6, 9, 10]. Therefore, gemcitabine is now combined with a platinum anti-cancer drug (cisplatin or carboplatin) to treat advanced UC worldwide. However, the disease progresses within a few years after chemotherapy in most patients. Therefore, identifying a prognostic factor for advanced UC would allow a better choice of therapeutic approach. The role of the immune system on disease cessation or progression has been investigated, and some hematological parameters are known prognostic factors for various types of carcinoma [12-16]. We assessed the prognostic values, hematological parameters (neutrophil, lymphocyte, and platelet counts; and hemoglobin, C-reactive protein, and albumin levels), and pain scores as well as Eastern Cooperative Oncology Group performance status (ECOG PS) in patients with advanced UC before starting GC therapy.

MATERIAL AND METHODS

Patients' characteristics

The clinical records of 30 patients with advanced UC who underwent GC therapy at our institution between December 2004 and March 2011 were retrospectively reviewed. All patients had a histological or cytological diagnosis of advanced UC, and had measurable lesions diagnosed using computed tomography (CT) or magnetic resonance imaging (MRI). The eligibility criteria comprised an ECOG PS of ≤2 and life expectancy of >3 months. If patients aged >80 years specifically requested chemotherapy, we included them in this study. Prior radiotherapy was permitted but must have been completed at least 6 weeks before starting therapy. None of the patients had any inflammatory diseases before starting GC therapy. All patients provided written informed consent to participate in this study, and proceeded in accordance with the Declaration of Helsinki and with good clinical practice guidelines.

Table 1 shows the characteristics of the 23 males and 7 females with a median age of 72 (range, 52-83) years. Of the patients, 23/30 (76.7%) had previously received MEC chemotherapy. One

patient had received etoposide and cisplatin and two had received radiotherapy and intraarterial chemotherapy. Four patients received gemcitabine and platinum anti-cancer drug as first-line chemotherapy against advanced disease. Primary urothelial tumor sites were located at the bladder in 9/30 (30%) patients and at the renal pelvis-ureter in 21/30 (70.0%) patients. The major metastatic sites comprised the lymph nodes in 18/30 (60%) patients, the lungs in 6/30 (20.0%) patients, bone in 2/30 (6.7%) patients, and local recurrence in 5/30 (16.7%) patients. At pretreatment assessment, 7/30 (23.3%) patients had metastatic or locally advanced disease at the primary site, and 23/30 (76.7%) patients had relapsed disease, and 19/30 (63.3%) patients had evaluable recurrent lesions after radical operation. A clinical history was obtained at the pre-treatment evaluation and each patient underwent a physical examination (including ECOG PS and pain score), including an automated blood cell count, biochemical profile, ECG, chest X-ray, and radiographic imaging studies that demonstrated typical areas of the target disease. Responses to chemotherapy were evaluated every one or two treatment cycles using radiographic imaging. The clinical response was evaluated using the response evaluation criteria in solid tumors (RECIST) [17]. All patients were followed up until death or loss to follow-up. Cancer-specific survival (CSS) was measured from the administration of the first dose until the last clinical visit or death due to UC. Variables included: age; sex; ECOG PS; primary tumor site; histology grade; administerd drugs; pretreatment hemoglobin level; neutrophil, lymphocyte, and thrombocyte counts; the NLR (neutrophil-lymphocyte ratio); the PLR (platelet-lymphocyte ratio); levels of serum albumin and serum CRP; and pain score.

Combination chemotherapy regimen

The creatinine clearance (CCr) (mL/min) of each patient was determined before starting the first cycle of this therapy.

Table 1. Patients' characteristics

Characteristics	No. of patients	(%)
No. of patients	30	(100)
Median age, yr (range)	72	(52-83)
Gender Male /Female	23/7	(76.7/23.3)
Previous therapy		
None	4/30	(13.3)
Methotrexate / Epirubicin / Cisplatin (MEC)	14/30	(46.7)
Methotrexate / Epirubicin / Carboplatin (modified MEC)	9/30	(30.0)
Etoposide / Cisplatin	1/30	(3.3)
Radiation + Intra-arterial chemotherapy	2/30	(6.7)
Primary urothelial tumor site		
Bladder	9/30	(30.0)
Renal pelvis-ureter	21/30	(70.0)
Advanced disease at first visit	7/30	(23.3)
Recurrence after surgery for primary tumor	21/30	(76.7)
Site of metastasis or recurrence, or invasion from primary tumor		
Lung	6/30	(20.0)
Lymph node	18/30	(60.0)
Local recurrence	5/30	(16.7)
Bone	2/30	(6.7)

Table 2. Patients' treatment profiles and efficacy

		No. of patients	(%)
No. of chemotherapy cycles	1	6/30	(20.0)
	2	8/30	(26.7)
	More than 3	16/30	(53.3)
Platinum drug	Cisplatin	12/30	(40.0)
	Carboplatin	18/30	(60.0)
Effects according to RECIST	CR	2/30	(6.7)
	PR	7/30	(23.3)
	SD	10/30	(33.3)
	PD	9/30	(30.0)
	NE	2/30	(6.7)
Outcome	NED	2/30	(6.7)
	Alive with cancer	8/30	(26.7)
	Dead due to cancer	20/30	(66.6)

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable

Cisplatin (70 mg/m^2) was administered intravenously (i.v.) for 30-60 min on day-2 when CCr ≥60 mL/min in the cisplatin group, and carboplatin (dose to an AUC of 5) was administered i.v. for 30-60 min to patients with a lower CCr on day-2 in the carboplatin group.

Gemcitabine (1000 mg/m^2) was administered i.v. for 30 min over a 28-day period (1 cycle) comprising three consecutive weeks of treatment (administration on days 1, 8, and 15) followed by one off-treatment week. This cycle was repeated, but a physician in charge who assessed the adverse events associated with the treatment as severe may have extended the number of days in each cycle.

Statistical analysis

We dichotomized continuous variables into two categories for statistical analysis including: age ≥70 (n = 19) and <70 (n = 11) years; ECOG PS ≥1 (n = 9) and 0 (n = 21); primary tumor site, renal pelvis-ureter (n = 21) and bladder (n = 9); histology grade, 3 (n = 22) and 2 (n = 6); drug, cisplatin (n = 12) and carboplatin (n = 18); serum hemoglobin level ≥10.1 (n = 21) and <10.1 (n = 9) mg/dL; neutrophil count, ≥4,000 (n = 8) and <4,000 (n = 22)/μL; lymphocyte count ≥1,200 (n = 17) and <1,200 (n = 13)/μL; thrombocyte count, ≥250,000 (n = 11) and <250,000 (n = 19)/μL; NLR ≥3.0 (n = 10) and <3.0 (n = 20); PLR ≥250 (n = 11) and <250 (n = 19); serum albumin, ≥3.5 (n = 22) and <3.5 (n = 8) g/dL; serum CRP ≥1.0 (n = 10) and <1.0 (n = 20) mg/dL; and pain positive (n = 6) and negative (n = 24). Cumulative survival scores were calculated using the Kaplan-Meier method, and differences in survival rates were analyzed using the log-rank test. Significant differences in pretreatment peripheral blood values and pain scores that influenced CSS after GC therapy were assessed using univariate analysis. A Cox proportional hazards model with forward stepwise variable selection was used in multivariate tests of factors that were significant in the univariate analysis. All data were statistically analyzed using PASW Statistics, version 18 (SPSS Japan Inc., Tokyo, Japan). P <0.05 was considered to be statistically significant.

RESULTS

Treatment profiles and outcomes

Table 2 describes the treatment profiles and outcomes. The patients underwent a total of 82 cycles of GC therapy. The median

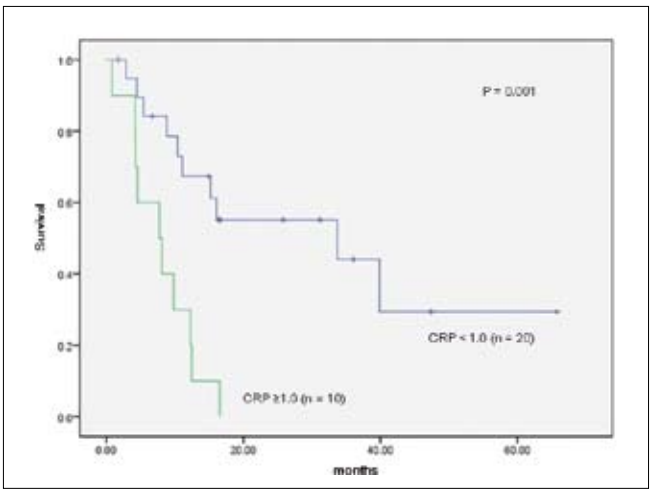

Fig. 1. Kaplan-Meier analysis of cancer-specific survival in patients with advanced UC stratified by levels of CRP before GC therapy.

number of consecutive cycles was three (range, one to seven) per patient. Of the patients, 16/30 (53.3%) underwent more than three cycles of therapy. The platinum anti-cancer drugs administered to 12/30 (40.0%) and 18/30 (60.0%) patients were cisplatin and carboplatin, respectively. Clinical outcomes and treatment effects were assessed in all 30 patients according to RECIST at the end of the study. Of the patients, 2/30 (6.7%) had no evidence of disease (NED), 8/30 (26.7%) remained alive with cancer, and 20/30 (66.6%) died as a result of the cancer. The RECIST findings of the effects of treatment were a complete response (CR) in 2/30 (6.7%) patients and a partial response (PR) in 7/30 (23.3%) for an overall response rate (ORR) of 30.0%. Stable (SD) and progressive (PD) disease was identified in 10/30 (33.3%) and 9/30 (30.0%) patients, respectively. One patient each with upper urinary tract cancer achieved CR for 38 and 66 months. The median CSS was 12.5 months (95% CI, 6.5-18.4). The 5-year CSS rate was about 20%. Table 2 shows peripheral blood values of the patients before GC therapy.

Analysis of survival

Figure 1 shows a significantly worse CSS in the group with high CRP than with low CRP (P = 0.001). Among the other factors, low albumin (P = 0.008), low hemoglobin (P = 0.025), and pain (P = 0.002) were associated with poorer CSS rates (Table 3). Survival rates did not significantly differ between patients given either cisplatin or carboplatin. Multivariate analysis of factors before GC therapy showed that serum CRP was an independent significant predictor for CSS, with a hazard ratio of 4.608 (95% CI, 1.763-12.047; P = 0.002).

Table 3. Patients' hematological values before GC therapy

Variables	Means ±SD	Median	Range
Hemoglobin (mg/dL)	11.00 ±1.774	11.05	7.5-16.9
Neutrophils (/μL)	4124.63 ±3489.63	3378.50	1645.00-21375.00
Lymphocytes (/μL)	1352.07 ±512.26	1334.00	441.00-2523.00
Thrombocytes (/μL)	281333 ±111375	236000	168000-602000
NLR	3.64 ±3.63	2.58	1.27-19.00
PLR	246.55 ±169.74	187.68	87.09-945.58
Albumin (g/dl)	3.73 ±0.57	3.75	2.40-4.80
CRP (mg/dl)	1.59 ±3.07	0.41	0.03-10.90

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; SD: standard deviation; CRP: C-reactive protein

Table 4. The characteristics of patients treated with GC therapy; univariate and multivariate analysis of CSS

Variable, category	Number of patients	Univariate P value	Multivariate HR (95% CI) P value
Age ≥ *vs.* <70 y	19/11	0.988	–
Male *vs.* female	23/7	0.591	–
ECOG PS, ≥1 *vs.* 0	9/21	0.661	–
Primary site, renal pelvis-ureter *vs.* bladder	21/9	0.519	–
Histology, Grade 3 *vs.* 2	22/6	0.876	–
Cisplatin *vs.* carboplatin	12/18	0.330	–
Hemoglobin, ≥ *vs.* <10.1 mg/dL	21/9	0.025	–
Neutrophils ≥ *vs.* <4,000 /μL	8/22	0.589	–
Lymphocytes ≥ *vs.* <1,200 /μL	17/13	0.776	–
Thrombocytes ≥ *vs.* <250,000 /μL	11/19	0.537	–
NLR ≥ *vs.* <3.0	10/20	0.063	–
PLR ≥ *vs.* < 50	11/19	0.843	–
Albumin ≥ *vs.* <3.5 g/dL	22/8	0.008	–
CRP ≥ *vs.* <1.0 mg/dL	10/20	0.001	4.608 (1.763-12.047) 0.002
Pain, positive *vs.* negative	6/24	0.002	–

HR: hazard ratio, CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance status, CSS: cancer-specific survival

DISCUSSION

In most patients, UC progresses after chemotherapy within a few years. Therefore, identifying a prognostic factor for advanced UC would allow a better therapeutic approach.

Most patients do not have inflammatory diseases before starting chemotherapy, but a systemic inflammatory response is associated with a poor prognosis in patients with various malignancies [12-16]. We usually collect peripheral blood data, pain score, and EOCG PS before starting chemotherapy, and we examine whether these routine data can predict prognoses. Although pretreatment NLR is associated with poor survival rates for patients with hepatocellular carcinoma, gastric cancer and renal cell carcinoma, the present study found no statistical differences in survival rates associated with NLR [12, 15, 16]. Although pretreatment PLR is also associated with poor survival rates among patients with pancreatic adenocarcinoma, the present study found no statistically significant difference [18].

Serum CRP is a representative marker of systemic inflammatory response and increased CRP is a poor prognostic factor for several types of cancer [19-22]. Proinflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor, and IL-6 induce CRP production in the liver [23]; a high serum CRP level before GC therapy predicted a poor prognosis for our patients with advanced UC. However, a high serum CRP level might simply reflect a non-specific inflammatory response secondary to tumor necrosis or local tissue damage. Miki et al. correlated an elevated CRP level with tissue IL-6 concentrations in tumors and speculated that such elevation predicted recurrent disease and shorter survival among patients with colorectal carcinoma [24]. They also described that an

IL-6/IL-6 receptor autocrine loop in colorectal carcinoma creates a local environment that favors tumor growth. Okamoto et al. found the same mechanism in urothelial carcinoma [25].

Paclitaxel and docetaxel have recently been studied as chemotherapeutic agents for patients who have previously been treated for advanced UC. The response rates to paclitaxel-based regimens combined with either carboplatin or cisplatin are between 16% and 36% with median overall survival ranging from 6 to 10 months [26, 27]. Furthermore, one study found an extremely promising response rate of 70% and a median survival of 14 months despite 55% of patients having visceral metastases treated with trastuzumab, paclitaxel, carboplatin, and gemcitabine [28]. One phase II trial found that sunitinib has antitumor activities against UC [29]. Another novel approach using molecular targeted therapy for advanced UC is bevacizumab combined with chemotherapeutic agents. A phase II study of bevacizumab combined with cisplatin and gemcitabine revealed a complete response in 19% of patients and a partial response in 53% of patients with metastatic or locally advanced UC, and a phase III trial of this combination is presently underway [30]. Despite the development of new chemotherapeutic agents, many patients with advanced UC still die within a few years of diagnosis. Because a high CRP level before GC therapy predicted a poor prognosis for patients with advanced UC in this study, we propose that such patients should receive psychiatric support from the start of GC therapy and they should be given second- or third-line chemotherapy or be encouraged to participate in clinical trials such as those of targeted therapies as soon as possible.

Because of the retrospective nature of this study and its limitation of small sample size, further larger, prospective studies are required to validate our findings. Serum CRP can be conveniently measured while obtaining blood cell counts and it can help to predict the survival of patients with advanced UC. Because peripheral blood analysis is rapid and simple, serum CRP might be a useful clinical biological marker, not only of a systemic inflammatory response, but also as a prognostic indicator for patients with advanced UC.

CONCLUSIONS

Elevated pretreatment serum CRP levels indicate a poor prognosis for patients undergoing GC therapy for advanced UC. We propose that such patients should receive second- or third-line chemotherapy or be encouraged to participate in clinical trials such as those of targeted therapies as soon as possible. Because of the limitation of the small sample size in our study, these results are only preliminary. However, these results seem to be very useful in clinical practice, further investigation with a larger number of patients is necessary to validate our findings.

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