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Cisplatin versus non-cisplatin based first-line chemotherapy for advanced urothelial carcinoma previously treated with peri-operative cisplatin

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Abstract

Introduction—The optimal choice of first-line chemotherapy in urothelial carcinoma (UC) patients who relapse after receiving peri-operative cisplatin-based chemotherapy (PCBC) is unclear. We investigated outcomes with cisplatin re-challenge vs. a non-cisplatin regimen in patients with recurrent metastatic UC following PCBC in a multicenter retrospective study.

Methods—Individual patient-level data were collected for patients who received various first-line chemotherapies for advanced UC following previous PCBC. Cox proportional hazards models were used to investigate the prognostic ability of type of peri-operative and first-line chemotherapy

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to independently impact overall survival (OS) and progression-free (PFS) after accounting for known prognostic factors.

Results—Data were available for 145 patients (12 centers). The mean age was 62 years; ECOG-PS was >0 in 42.0% patients. Sixty-three-percent of patients received cisplatin-based first-line chemotherapy and the median time from prior chemotherapy (TFPC) was 6.2 months (range 1–154). Median OS was 22 months (95%CI:18–27) and median PFS was 6 months (95%CI:5–7). Better ECOG-PS and longer TFPC (>12 months vs ≤12 months; HR 0.32, 95%CI: 0.20–0.52, p<0.001) was prognostic for OS and PFS. Cisplatin-based chemotherapy was associated with poor OS (1.86 [95% CI: 1.13, 3.06], p=0.015), which appeared to be pronounced in those patients with TFPC ≤12 months, re-treatment with cisplatin in the first-line setting was associated with worse OS (HR=3.38, p<0.001).

Conclusions—This retrospective analysis suggests that in patients who had received prior PCBC for UC, re-challenging with cisplatin may confer poorer OS, especially in those who progressed in less than a year.

Microabstract

To identify the optimal choice for first-line chemotherapy in advanced urothelial carcionoma (UC) we investigated outcomes with cisplatin vs. non-cisplatin regimens in patients with mtastastic UC following peri-operative cisplatin-based chemotherapy (PCBC) in a multicenter retrospective study. In patients who had received prior PCBC for UC, re-challenging with cisplatin conferred poorer overall survival, especially in those who progressed in less than one-year.

Keywords

cisplatin; first-line; peri-operative; urothelial carcinoma

Introduction

Despite relatively high initial response rates to chemotherapy, durability of response is still suboptimal, and 5-year survival rates for patients with metastatic urothelial carcinoma (UC) of the bladder is only 10–20% [1,2]. In both the peri-operative and first-line metastatic setting, cisplatin combination chemotherapy (predominantly gemcitabine and cisplatin (GC); or methotrexate, vinblastine, doxorubicin and cisplatin (MVAC)) is the standard of care [1–7]. For those patients who progress after receiving peri-operative cisplatin-based chemotherapy, however, there is no consensus as to whether cisplatin re-challenge or the use of a different regimen is superior. Clinical trials which established MVAC and GC as standard of care for metastatic therapy [1–5] were conducted in populations for whom peri-operative chemotherapy was either not yet an option or did not allow prior systemic therapy [8]. Yet contemporary trials evaluating these regimens in patients after PCBC are lacking. A key question therefore is: should advanced UC after PCBC be re-treated with cisplatin based chemotherapy or receive a different non-cisplatin or second-line regimen to improve efficacy.

To address this question we initiated a multicenter retrospective study to investigate differences in outcomes between patients with advanced UC who received cisplatin-based first-line chemotherapy versus those who did not receive cisplatin-based first-line

chemotherapy, following previous peri-operative (neoadjuvant or adjuvant) cisplatin-based chemotherapy (PCBC). It was hypothesized that patients with a long TFPC would be reflective of platinum-sensitive disease, and these patients would have improved outcomes with cisplatin-based chemotherapy in the first-line setting. Conversely, the therapeutic index may be better when using a non-cisplatin regimen in those with a short TFPC following PCBC.

Patients and Methods

Patient population

Individual patient-level data were collected from 12 regional referral centres in North America and Europe for consecutive patients who received chemotherapy for advanced UC after previous peri-operative cisplatin-based therapy. Data included age, sex, baseline visceral metastasis (defined as one or more of bone, brain, liver, lung), Eastern Cooperative Oncology Group (ECOG) performance status (PS), time from prior peri-operative chemotherapy (TFPC), calculated creatinine clearance, hemoglobin (Hb), leukocyte count, and albumin. Peri-operative and first-line chemotherapy treatment information, such as number of cycles of chemotherapy, dose of cisplatin per cycle, setting of peri-operative chemotherapy (neoadjuvant or adjuvant), and first-line regimen were also collected, along with patient outcomes, specifically objective response-rate (ORR), progression-free survival (PFS), and overall survival (OS), from first-line therapy. The study was conducted after approval from the ethics committee of the University of British Columbia (sponsor of the study) and of each participating Institutions.

Statistical analysis

Descriptive statistics were used to summarize patient and treatment characteristics and outcomes. The study endpoints were PFS and OS. OS was the primary clinical endpoint of interest and defined as the time between the start of first-line therapy and death from any cause; time was censored at the date of last follow-up for patients remaining alive. PFS was the time between the start of first-line therapy and the date of disease progression or death without progression, whichever occurred first; time was censored at the date of last follow-up for patients alive without progression, both defined from the date of beginning first-line chemotherapy. TFPC was defined from the last date of peri-operative chemotherapy until the first date of first-line therapy. Predefined cut points of TFPC were selected *a priori* at ~0.5 years (26 weeks), ~1 year (52 weeks), ~1.5 years (78 weeks), and ~2 years (104 weeks) for analysis. Anemia was defined as Hb < the lower limit of normal recorded by the local laboratory. Leukocytosis was defined as a white blood cell count (WBC) > the upper limit of normal (ULN) based on the local laboratory. Albumin was evaluated on a continuous scale.

The Kaplan–Meier method was used to estimate time to event outcomes. Univariate Cox proportional hazards models were used to investigate the prognostic ability of all factors and clinical trial status (i.e. whether therapy was on trial or not) on OS and PFS. The effect of treatment for metastatic disease (cisplatin-based chemotherapy versus non-cisplatin-based chemotherapy) and specific peri-operative chemotherapy (GC, MVAC or others) was investigated univariably, and in a multivariable model after adjusting for 4 known prognostic

factors; ECOG-PS (≥1 versus 0), anemia, visceral metastases, and TFPC. Attempts to identify optimal cut points for TFPC were performed by examining martingale residuals, and evaluating results from multiple models based on TFPC as a log-transformed continuous covariable, and using the *a priori* defined cut points. All tests and confidence intervals (CIs) were 2-sided and statistical significance was defined at $P = 0.05$ level.

Results

Patient characteristics

Patient and treatment characteristics are summarized in Table 1. One-hundred and forty-five patients treated from 1995–2014 (exception: 2007–2011 for UAB Comprehensive Cancer Center) were included from 12 institutions in North America and Europe. The median (range) age of patients was 63 (32–81) years at first-line, over three-quarters of patients were male, and 10.4% were ECOG PS 2 or 3. Most patients (n=90, 63.8%) received adjuvant chemotherapy. Eighty-one (57.5%) patients received GC peri-operative chemotherapy, 36 (25.5%) received MVAC, and 24 (17%) received another cisplatin-based regimen. These other cisplatin-based regimes consisted of 11 patients who received methotrexate, vinblastine, epirubicin, cisplatin, and 9 who received methotrexate, cisplatin and the remaining 4 patients received another cisplatin-based combination. Ninety-one (62.8%) were retreated with cisplatin-based first-line chemotherapy (cisplatin with etoposide, methotrexate, vinblastine, gemcitabine or doxorubicin) and 12 (8.3%) received first-line therapy as part of a clinical trial. Clinical trial therapies included AZD4877, OGX427, PZP, ramucirumab, sunitinib, vinflunine, vinblastine, nab-paclitaxel. The remaining 42 (28.9%) patients received non-cisplatin-based first-line therapy regimes including carboplatin with vinblastine, paclitaxel or gemcitabine, paclitaxel with gemcitabine or everolimus, ramucirumab with docetaxel docetaxel alone, paclitaxel alone. Median (IQR) TFPC was 7 (1 to 19) months. Since only 24 (17.0%) patients had TFPC > 2 years, the use of 2 years as a cut point was excluded from future analyses. After a median follow up of 10.8 (IQR: 5.5–18.9) months, 136 (94%) patients had confirmed disease progression, and 104 (71.7%) patients have died. One-year PFS and OS were 22.7% (95%CI: 16.1 to 29.9) and 73.8% (95%CI: 65.3 to 80.5), respectively.

Association of variables with OS

The results of the univariate and multivariable Cox analyses on OS are presented in Tables 2 and 3, respectively. In the univariate analysis, the type of peri-operative chemotherapy (GC: HR=1.54, 95% CI=0.95 to 2.49, MVAC: HR=0.81, 95% CI=0.41 to 1.61, overall p=0.046), TFPC (26-week cut point: HR=0.50, 95% CI=0.33 to 0.74, p<0.001; 12 months: HR=0.42, 95% CI 0.27 to 0.65, p<0.001; 20 months: HR=0.40, 95% CI=0.25 to 0.65, p<0.001; log-transformed: HR=0.85, 95% CI=0.76 to 0.95, p=0.005) and age at first-line therapy (HR=0.97, 95% CI=0.95 to 1.00, p=0.025) were all statistically significant. Figure 1 shows the OS for patients based on TFPC >52 versus ≤12 months.

After adjusting for ECOG-PS, TFPC, anemia status and presence of visceral metastases, first-line cisplatin-based chemotherapy was a statistically significant poor prognostic factor

for OS (HR=1.86, 95% CI=1.13 to 3.06; p=0.015). No significant interaction was observed between cisplatin-based treatment and TFPC at 12 months (p=0.30) or 18 months (p=0.52).

The interaction term between cisplatin treatment and TFPC was not statistically significant (p=0.61), however, the estimated HR for cisplatin treatment amongst patients with TFPC ≤12 months was 1.14, indicative of worse outcome for those treated with cisplatin. In contrast, the HR for cisplatin treatment amongst patients with TFPC >12 months was 0.75, indicative of improved outcomes amongst cisplatin treated patients. For those patients with TFPC ≤12 months, re-treatment with cisplatin in the first-line setting was associated with statistically significantly worse (HR=3.38, p<0.001) OS, while the effect was reduced (HR=1.88) and non-significant (p=0.14) amongst patients with TFPC >12 months (see Table 3 and Figure 2).

Association of variables with PFS

The results of univariate and multivariable Cox analyses on PFS are shown in Tables 4 and 5, respectively. In the univariate analysis, TFPC using the 78-week cut point (Hazard Ratio (HR)=0.58, 95% Confidence Interval (CI)=0.38 to 0.89, p=0.013), ECOG-PS (HR=1.69, 95% CI=1.19 to 2.42, p=0.004), WBC (HR=1.52, 95% CI=1.06 to 2.16, p=0.022), clinical trial status (HR=2.00, 95% CI=1.07 to 3.74, p=0.030) and peri-operative chemotherapy type (GC HR=0.95, 95% CI=0.60 to 1.50; MVAC HR=0.47, 95% CI=0.27 to 0.82, versus other cisplatin-based chemotherapies, p-value=0.005) were all statistically significant. The effect of peri-operative chemotherapy type on PFS was evaluated adjusting for first-line ECOG-PS with similar results (data not shown). No obvious cut point for TFPC was observed after examining martingale residual plots, and no interaction between TFPC at either 12 months (p-value=0.59) or 18 months (p-value=0.53) with cisplatin first-line therapy was observed, so 1-year was selected based on practical considerations. After adjusting for ECOG-PS, site of metastases, anemia and TFPC, type of first-line chemotherapy (cisplatin vs. non-cisplatin) was not statistically significantly associated with PFS (HR=0.92, 95% CI=0.61 to 1.40, p=0.70 for cisplatin-based chemotherapies). The estimated HR for PFS was >1 for patients with TFPC ≤12 months, while it was <1 for those patients with TFPC >12 months (Table 5).

Discussion

The optimal selection of chemotherapy for recurrent metastatic UC following prior peri-operative cisplatin-based chemotherapy remains a significant area of uncertainty [9–11]. Specifically, the impact of reinstituting cisplatin-based combination chemotherapy versus a different noncisplatin-based first-line combination chemotherapy regimen versus a second-line generally single agent therapy is unclear. This retrospective study including 145 patients from 12 different institutions aimed to shed light on this issue. The study assembled patients treated at multiple institutions, because of the difficulty of identifying a large cohort of such patients from a single institution. As this is a retrospective analysis, the analyses accounted for the impact of known prognostic factors in the first-line and/or salvage settings, notably presence of visceral disease, hemoglobin (Hb) level, patient performance status, leukocytosis, albumin and time from prior peri-operative chemotherapy (TFPC) were incorporated in this analysis based on their demonstrated prognostic impact in previous

reports [12–14]. The major finding of our study is that reinstituting cisplatin-based first-line chemotherapy after PCBC may have a detrimental impact on OS, especially on those within 12 months of prior therapy. However, cisplatin-based first-line chemotherapy was not associated with poorer PFS. Nevertheless, these data cast doubts on the viability and utility of reinstituting cisplatin-based first-line chemotherapy in those previously exposed to PCBC.

Interestingly, the type of peri-operative chemotherapy was observed to be a significant prognostic factor for OS and PFS on univariate analyses only, although we hasten to point out that this may well be resultant of patient selection factors. Patients treated with peri-operative GC had a worse prognosis compared with patients treated with MVAC. Since GC is more tolerable than MVAC, the latter may select for patients with a better initial health status and fewer comorbidities. Other factors (e.g. social support) could not be captured in this retrospective review, and likely also confound the interpretation of this result.

Not unexpectedly, previously recognized prognostic factors such as time from peri-operative chemotherapy to first-line therapy and ECOG-PS were significant prognostic factors for both OS and PFS [14–16]. In contrast, Hb and sites of metastasis were not significant on multivariable analyses, which may be a consequence of small sample size and an underpowered analysis.

Interpretation of results from this study is limited due to its retrospective nature and modest sample size. First and foremost, numerous reasons are considered when determining a type of first-line chemotherapy for patients, much of which cannot be captured in a retrospective chart review such as this analysis. Prospective validation, ideally through a clinical trial, is necessary to determine the optimal treatment, however the relatively low prevalence that this population represents will likely preclude such a possibility. The proportion and number of patients receiving non-cisplatin-based therapy for metastatic recurrence was relatively modest and the types of non-cisplatin agents were quite varied and were categorized together. This raises the likelihood that the efficacy of specific non-cisplatin drug regimens were masked. As is common in many retrospective analyses, missing data was common, which limited the ability to explore the effects of some factors such as albumin and baseline neutrophil-lymphocyte ratio (NLR). WBC was evaluated instead of baseline neutrophil-lymphocyte ratio (NLR), which is known to demonstrate prognostic capability in several oncological settings. The cause for poorer OS when repeating cisplatin-based first-line therapy after PCBC is unclear and requires further study. Lastly, some patients may choose other treatments, such as palliative care or a non-chemotherapy based clinical trial; which may limit the generalizability of these results.

Given our results, there remains some uncertainty on whether or not one should re-challenge a patient with cisplatin-based first-line therapy; however, given that the majority of patients in our dataset had recurred within 1 year of PCBC, patients relapsing <1 year after peri-operative cisplatin-based chemotherapy should probably be considered for alternative non-cisplatin or second-line treatments or clinical trials. Notably, all of the landmark phase III trials that evaluated cisplatin-based first-line chemotherapy did not include patients who had received PCBC [2,4,17,18]. One prior retrospective study suggested that repeating cisplatin after

>1 year from PCBC may be reasonable, although that study did not assess a differential impact of other non-cisplatin-based regimens on disease recurrence [15].

Our findings suggest that the therapeutic index of cisplatin-based first-line chemotherapy following PCBC is suboptimal. Moreover, durable complete remission by repeating cisplatin-based chemotherapy is biologically unlikely in those who recurred following PCBC. Indeed, residual renal dysfunction following PCBC may render many patients suboptimal candidates for re-challenging with cisplatin. Assuming that most appropriate and fitter cisplatin-eligible patients received first-line cisplatin (and only cisplatin-ineligible patients or those with comorbidities or poor performance received other regimens), it is somewhat worrisome that those receiving first-line cisplatin demonstrated poor OS. Thus, with the exception of those with a long time from PCBC (>12 months) and no residual toxicities of cisplatin such as renal dysfunction and neurotoxicity, re-challenging with cisplatin should probably not be considered.

Conclusions

This hypothesis-generating retrospective analysis demonstrated that re-challenging patients who progressed following PCBC for UC, especially those progressing within a year, with cisplatin appears ill advised. Further validation in a larger dataset is warranted.

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Clinical Practice Points

1. The optimal selection of chemotherapy for recurrent metastatic UC following prior peri-operative cisplatin-based chemotherapy remains a significant area of uncertainty.
2. In a multicenter retrospective study we demonstrate that reinstituting cisplatin-based first-line chemotherapy after PCBC may have a detrimental impact on OS, especially on those within one year of prior therapy.
3. In future practice, these results cast doubts on the viability and utility of reinstituting cisplatin-based first-line chemotherapy in those previously exposed to PCBC.

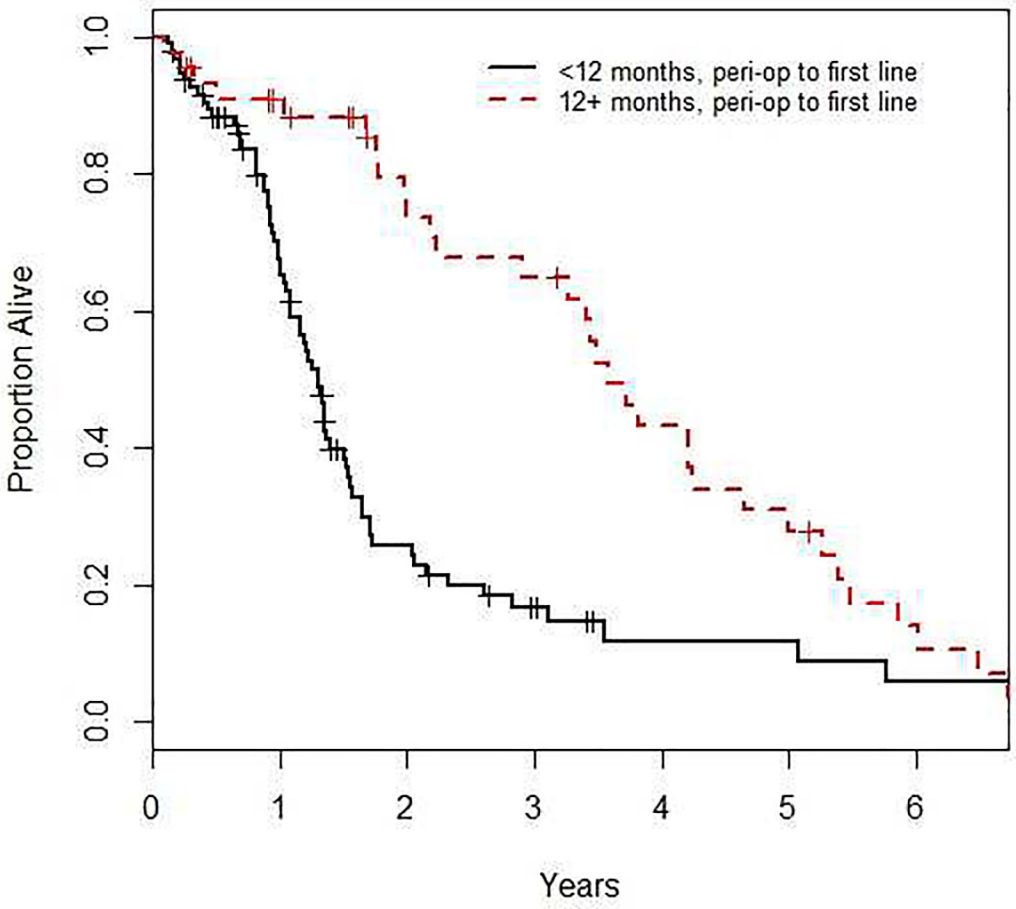

Figure 1.

shows the effect of TFPC on OS when patients are subcategorized into <12 months and 12+ months. Time from peri-operative chemotherapy to first-line chemotherapy was significantly prognostic for OS (HR 0.39, 95% CI, 0.21, 0.75, p=0.004). Analyses were adjusted for ECOG status, presence of visceral metastases and hemoglobin.

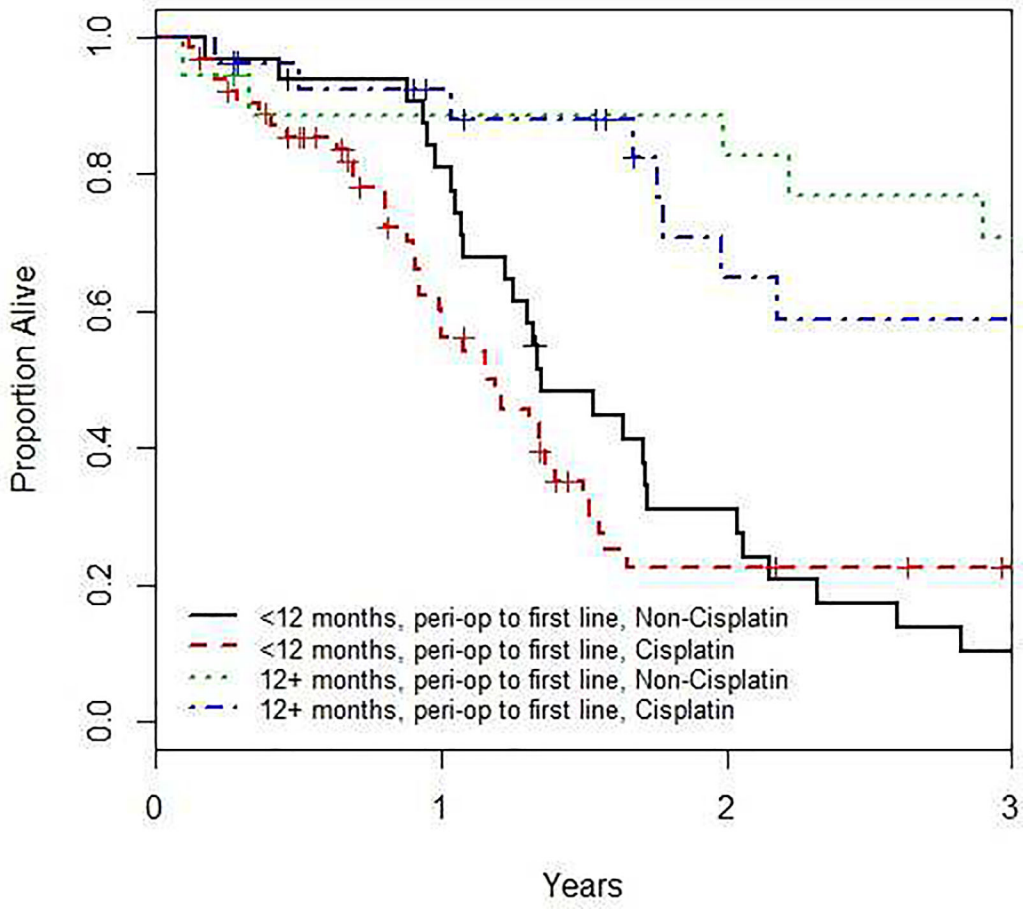

Figure 2.

shows the effect of TFPC on OS when patients are subcategorized into <12 months, 12+ months, first-line cisplatin and first-line non-cisplatin. Time from peri-operative chemotherapy to first-line chemotherapy was significantly prognostic for OS regardless of whether first-line cisplatin was used (HR 0.421, 95% CI 0.23, 0.76, p=0.004) or not (HR 0.39, 95% CI 0.21, 0.75, p=0.004).

Table 1

Patient Characteristics

Variable	Total Patients	Overall (n = 145)	Cisplatin (n = 91)	Other (n = 54)	*P* Value
Institution	145				NS
AOU Frederico II + Napoli		13 (9.0)	13 (14.3)	0 (0.0)	
BCCA		21 (14.5)	17 (18.9)	4 (7.4)	
CCI		11 (7.6)	10 (11.0)	1 (1.9)	
COH		3 (2.1)	3 (3.3)	0 (0.0)	
Dusseldorf		5 (3.5)	2 (2.2)	3 (5.6)	
AUO 20/99 (GemTax)		35 (24.1)	0 (0.0)	35 (64.8)	
INT		44 (30.3)	38 (41.8)	6 (11.1)	
Karmanos		5 (3.5)	1 (1.1)	4 (7.4)	
Liverpool		1 (0.7)	1 (1.1)	0 (0.0)	
UAB		4 (2.8)	3 (3.3)	1 (1.9)	
Utah		3 (2.1)	3 (3.3)	0 (0.0)	
Male gender	145	113 (77.9)	71 (78.0)	42 (77.8)	.97
Perioperative chemotherapy	141				.063
Neoadjuvant-based		51 (36.2)	38 (41.8)	13 (26.0)	
Adjuvant-based		90 (63.8)	53 (58.2)	37 (74.0)	
Perioperative chemotherapy type	141				<.001
GC		81 (57.5)	60 (65.9)	21 (42.0)	
MVAC		36 (25.5)	30 (33.0)	6 (12.0)	
Other cisplatin-based[b]		24 (17.0)	1 (1.1)	23 (46.0)	
Cycles (n)	140				<.001
1		20 (14.3)	16 (17.8)	4 (8.0)	
2		29 (20.7)	27 (30.0)	2 (4.0)	
3		36 (25.7)	16 (17.8)	20 (40.0)	
4		46 (32.9)	23 (31.1)	18 (36.0)	
5		2 (1.4)	0 (0.0)	2 (4.0)	

Variable	Total Patients	Overall (n = 145)	Cisplatin (n = 91)	Other (n = 54)	*P* Value
6		7 (5.0)	3 (3.3)	4 (8.0)	
Metastatic recurrence site: visceral disease	145	69 (47.6)	44 (48.4)	25 (46.3)	.81
Time from PCBC to first-line (mo)	141				.003
Median		6.2	2.3	8.1	
IQR		0.9–17.3	0.9–16.6	4.8–22.8	
TFPC	141				
>6 mo		72 (51.1)	40 (44.0)	32 (64.0)	.023
>12 mo		45 (31.9)	27 (29.7)	18 (36.0)	.44
>18 mo		32 (22.7)	18 (19.8)	14 (28.0)	.26
>24 mo		24 (17.0)	13 (14.3)	11 (22.0)	.24
Mean age at first-line therapy (year)	141	61.6 ± 8.8	61.1 ± 8.2	62.6 ± 9.7	.18
Weight at first-line therapy (kg)	94				.46
Median		76.8	77.5	74.5	
Range		49–140	50–140	49–123	
First-line chemotherapy[a]	145				
Cisplatin, no clinical trial		89 (66.9)	89 (97.8)	0 (0.0)	
Clinical trial		12 (8.3)	2 (2.2)	10 (18.5)	
Non-cisplatin, no clinical trial		44 (33.1)	0 (0.0)	44 (81.5)	
Frequency of first-line chemotherapy					.003
Every 2 wk	140	19 (13.6)	19 (20.9)	0 (0.0)	
Every 3 wk		116 (82.9)	69 (75.8)	47 (95.9)	
Every 4 wk		5 (3.6)	3 (3.3)	2 (4.1)	
No. of first-line cycles	137				.64
Median		4	4	4	
Range		1–17	1–8	1–17	
First-line therapy stopped by toxicity	139	31 (22.3)	21 (23.1)	10 (20.8)	.76
ECOG PS at first-line therapy	135				<.001
0		74 (54.8)	60 (67.4)	14 (30.4)	
1		47 (34.8)	21 (23.6)	26 (56.5)	

Variable	Total Patients	Overall (n = 145)	Cisplatin (n = 91)	Other (n = 54)	*P* Value
2		12 (8.9)	6 (6.7)	6 (13.0)	
3		2 (1.5)	2 (2.3)	0 (0.0)	
Creatinine clearance (mL/min)	126				.003
<60		38 (30.2)	17 (21.0)	21 (46.7)	
≥60		88 (69.8)	64 (79.0)	24 (53.3)	
Hemoglobin, normal range	138	78 (56.5)	45 (52.3)	33 (63.5)	.20
WBC count greater than ULN	131	65 (49.6)	29 (34.9)	36 (75.0)	<.001
Albumin	63				.64
Median		4	4	4.1	
Range		2.2–5.12	2.2–5.1	3.3–4.5	
Best overall response to first-line therapy	145				.29[c]
CR		18 (12.4)	11 (12.1)	7 (13.0)	
PR		47 (32.4)	22 (24.2)	8 (14.8)	
SD		30 (20.7)	17 (18.7)	20 (37.0)	
PD		37 (25.5)	5 (5.5)	8 (14.8)	
NE		13 (9.0)	36 (39.6)	11 (20.4)	
PFS	145				.12
Patients with progression		136 (93.8)	85 (93.4)	51 (94.4)	
Median PFS[d] (mo)		5.5 (4.1–6.2)	6.0 (5.5–7.4)	3.5 (2.1–5.1)	
6-mo PFS (%)		43.1 (34.8–51.1)	49.4 (38.7–59.3)	32.6 (20.5–45.2)	
12-mo PFS (%)		22.7 (16.1–29.9)	24.1 (15.8–33.5)	20.4 (10.7–32.3)	
24-mo PFS (%)		8.7 (4.6–14.3)	9.5 (4.4–17.0)	7.6 (2.3–17.5)	
OS	145				.18
Patients who died		104 (71.7)	58 (63.7)	46 (85.2)	
Median OS[d] (mo)		19.8 (16.1–24.4)	18.0 (13.8–21.4)	23.7 (16.1–33.8)	
6-mo OS (%)		89.2 (82.7–93.3)	87.5 (78.5–92.9)	92.2 (80.5–97.0)	
12-mo OS (%)		73.8 (65.3–80.5)	70.4 (59.0–79.1)	83.8 (70.2–91.6)	
24-mo OS (%)		41.5 (32.4–50.4)	36.0 (24.6–47.6)	49.7 (34.9–62.9)	

Variable	Total Patients	Overall (n = 145)	Cisplatin (n = 91)	Other (n = 54)	*P* Value
60-mo OS (%)		17.1 (10.3–25.4)	13.8 (5.5–25.6)	20.9 (10.5–33.6)	

Data presented as n (%), mean ± standard deviation, or rate (95% CI), unless otherwise noted. Abbreviations: AOU Frederico II + Napoli = University of Naples; AUO = Azienda Ospedaliera Universitaria; BCCA = British Columbia Cancer Agency; CCI = Cross Cancer Institute; CI = confidence interval; COH = City of Hope Cancer Center; CR = complete response; Dusseldorf = Heinrich Heine University; ECOG = Eastern Cooperative Oncology Group; GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; INT = Fondazione IRCCS Istituto Nazionale dei Tumori; IQR = interquartile range; Karmanos = Barbara Ann Karmanos Cancer Institute; Liverpool = University of Liverpool; NE = not evaluable; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PS = performance status; SD = stable disease; TFPC = time from previous chemotherapy; UAB = UAB Comprehensive Cancer Center; ULN = upper limit of normal; Utah = Huntsman Cancer Institute; WBC = white blood cell.

[a]First-line chemotherapy: cisplatin-based—cisplatin with etoposide, methotrexate, vinblastine, and gemcitabine or doxorubicin; clinical trial-based—, OGX427, PZP, ramucirumab, sunitinib, VFL ×2, vinblastine, vinflunine ×3, nab-paclitaxel; non—cisplatin-based—carboplatin with vinblastine, paclitaxel, or gemcitabine; paclitaxel with gemcitabine or everolimus; ramucirumab with docetaxel; docetaxel alone; paclitaxel alone.

[b]Other cisplatin-based = methotrexate, vinblastine, epirubicin, cisplatin (n = 11), methotrexate, cisplatin (n = 9), various combinations (n = 4).

[c]Response versus no response.

[d]Data in parentheses are 95% CIs.

Table 2.

Prognostic Factors for OS (Univariate)

Factor		N	Hazards Ratio (95% CI)	p-value
Gender	Female vs Male	145	0.78 (0.49, 1.27)	0.32
Peri-operative Chemo	Adjuvant vs Neoadjuvant	141	0.80 (0.53, 1.21)	0.29
Peri-operative Chemo Type	GC	141	1.54 (0.95, 2.49)	0.046
	MVAC		0.81 (0.41, 1.61)	
	Other Cisplatin-Based		Reference	
Number of Cycles	Continuous	140	0.90 (0.76, 1.07)	0.23
Site of Metastases	Visceral Disease vs No	145	0.93 (0.63, 1.37)	0.70
Time Peri-op to first-line	Log-transformation	141	0.85 (0.76, 0.95)	0.005
	>6 vs ≤2		0.50 (0.33, 0.74)	<0.001
	>12 vs ≤12		0.42 (0.27, 0.65)	<0.001
	>18 vs ≤18		0.40 (0.25, 0.65)	<0.001
Age at first-line	Continuous	141	0.97 (0.95, 1.00)	0.025
Weight at first-line, kg	Continuous	94	1.00 (0.99, 1.01)	0.80
ECOG Status at first-line	1+ vs 0	135	1.34 (0.89, 2.01)	0.16
Creatinine Clearance	≥60 ml/min vs <60	126	0.76 (0.50, 1.16)	0.20
Hemoglobin	In Normal Range vs No	138	1.06 (0.71, 1.57)	0.78
WBC	>ULN vs No	131	1.11 (0.75, 1.65)	0.61
Albumin	Continuous	63	0.60 (0.36, 1.01)	0.057
First-line Chemotherapy	Cisplatin	145	1.32 (0.88, 1.97)	0.18
First-line Chemotherapy	Clinical Trial	145	1.35 (0.65, 2.79)	0.42

Factor		N	Hazards Ratio (95% CI)	p-value
Frequency of first-line Chemotherapy	Ordinal	140	0.91 (0.43, 1.91)	0.80
First-line Non-Cisplatin Patients*				
Time Peri-op to first-line	>12 vs ≤12 months	50	0.39 (0.21, 0.75)	0.004
Time Peri-op to first-line	>18 vs ≤18 months	50	0.40 (0.21, 0.78)	0.007
First-line Cisplatin Patients*				
Time Peri-op to first-line	>12 vs ≤12 months	91	0.42 (0.23, 0.76)	0.004
Time Peri-op to first-line	>18 vs ≤18 months	91	0.39 (0.19, 0.78)	0.008

* Interaction term between cisplatin status and time from peri-op to first-line therapy was not significant (12 months p=0.92 and 20 months p=0.89).

Table 3.

Prognostic Factors for OS (Multivariable)

Factor		N	Hazards Ratio (95% CI)	p-value
All Patients†*				
ECOG Status at first-line	1+ vs 0	128	2.24 (1.36, 3.69)	0.002
Site of Metastases	Visceral Disease vs No		0.83 (0.55, 1.25)	0.38
Hemoglobin	In Normal Range vs No		0.77 (0.49, 1.21)	0.26
Time Peri-op to first-line	>12 vs ≤12 months		0.32 (0.20, 0.52)	<0.001
First-line Chemotherapy	Cisplatin		1.86 (1.13, 3.06)	0.015
TFPC ≤12 months				
ECOG Status at first-line	1+ vs 0	85	4.50 (2.26, 8.97)	<0.001
Site of Metastases	Visceral Disease vs No		0.94 (0.57, 1.57)	0.82
Hemoglobin	In Normal Range vs No		0.91 (0.53, 1.54)	0.71
First-line Chemotherapy	Cisplatin		3.38 (1.66, 6.89)	<0.001
TFPC >12 months				
ECOG Status at first-line	1+ vs 0	43	1.38 (0.62, 3.05)	0.43
Site of Metastases	Visceral Disease vs No		0.96 (0.44, 2.13)	0.93
Hemoglobin	In Normal Range vs No		0.58 (0.23, 1.45)	0.24
First-line Chemotherapy	Cisplatin		1.88 (0.82, 4.35)	0.14

†Addition of clinical trial status as a factor was not significant (p=0.22).

*Interaction term between cisplatin status and time from peri-op to first-line therapy was not significant (p=0.30).

Table 4.

Prognostic Factors for PFS (Univariate)

Factor		N	Hazards Ratio (95% CI)	p-value
Gender	Female vs Male	145	0.76 (0.50, 1.15)	0.19
Peri-operative Chemo	Adjuvant vs Neoadjuvant	141	1.03 (0.72, 1.47)	0.88
Peri-operative Chemo Type	GC	141	0.95 (0.60, 1.50)	0.005
	MVAC		0.47 (0.27, 0.82)	
	Other Cisplatin-Based		Reference	
Number of Cycles	Continuous	140	1.00 (0.88, 1.15)	0.95
Site of Metastases	Visceral Disease vs No	145	0.90 (0.64, 1.26)	0.52
Time Peri-op to first-line	Log-transformed	141	0.97 (0.88, 1.07)	0.58
	>6 vs ≤6		0.90 (0.63, 1.26)	0.53
	>12 vs ≤12		0.73 (0.50, 1.06)	0.094
	>18 vs ≤18		0.58 (0.38, 0.89)	0.013
Age first-line	Continuous	141	0.98 (0.96, 1.00)	0.098
Weight at first-line, kg	Continuous	94	1.00 (0.98, 1.01)	0.61
ECOG Status at first-line	1+ vs 0	135	1.69 (1.19, 2.42)	0.004
Creatinine Clearance	≥60 ml/min vs <60	126	0.93 (0.63, 1.38)	0.71
Hemoglobin	In Normal Range vs No	138	0.94 (0.66, 1.32)	0.71
WBC	>ULN vs No	131	1.52 (1.06, 2.16)	0.022
Albumin	Continuous	63	1.02 (0.64, 1.63)	0.94
First-line Chemotherapy	Cisplatin	145	0.76 (0.53, 1.08)	0.12
First-line Chemotherapy	Clinical Trial	145	2.00 (1.07, 3.74)	0.030

Factor		N	Hazards Ratio (95% CI)	p-value
Frequency of first-line Chemotherapy	Ordinal	140	1.26 (0.72, 2.20)	0.42
First-line Non-Cisplatin Patients*				
Time Peri-op to first-line	>12 vs ≤12 months	50	0.88 (0.48, 1.60)	0.67
Time Peri-op to first-line	>18 vs ≤18 months	50	0.73 (0.39, 1.39)	0.34
First-line Cisplatin Patients*				
Time Peri-op to first-line	>12 vs ≤12 months	91	0.63 (0.39, 1.02)	0.059
Time Peri-op to first-line	>18 vs ≤18 months	91	0.46 (0.26, 0.82)	0.009

* Interaction term between cisplatin status and time from peri-op to first-line therapy was not significant (12 months p=0.59 and 20 months p=0.53).

Table 5.

Prognostic Factors for PFS (Multivariable)

Factor		N	Hazards Ratio (95% CI)	p-value
All Patients†*				
ECOG Status at first-line	1+ vs 0	128	1.73 (1.14, 2.62)	0.010
Site of Metastases	Visceral Disease vs No		1.01 (0.70, 1.47)	0.95
Hemoglobin	In Normal Range vs No		0.76 (0.52, 1.12)	0.16
Time Peri-op to first-line	>12 vs ≤12 months		0.63 (0.41, 0.95)	0.027
First-line Chemotherapy	Cisplatin		0.92 (0.61, 1.40)	0.70
TFPC ≤12 months				
ECOG Status at first-line	1+ vs 0	85	2.42 (1.44, 4.04)	<0.001
Site of Metastases	Visceral Disease vs No		0.91 (0.58, 1.44)	0.70
Hemoglobin	In Normal Range vs No		0.78 (0.48, 1.27)	0.33
First-line Chemotherapy	Cisplatin		1.14 (0.66, 1.95)	0.64
TFPC >12 months				
ECOG Status at first-line	1+ vs 0	43	1.09 (0.53, 2.26)	0.81
Site of Metastases	Visceral Disease vs No		1.17 (0.57, 2.40)	0.67
Hemoglobin	In Normal Range vs No		0.65 (0.32, 1.34)	0.24
First-line Chemotherapy	Cisplatin		0.75 (0.37, 1.52)	0.42

†Addition of clinical trial status as a factor was not significant (p=0.68).

*Interaction term between cisplatin status and time from peri-op to first-line therapy was not significant (p=0.61).