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ORIGINAL REPORT

Randomized Phase III Study Comparing Paclitaxel/Cisplatin/Gemcitabine and Gemcitabine/Cisplatin in Patients With Locally Advanced or Metastatic Urothelial Cancer Without Prior Systemic Therapy: EORTC Intergroup Study 30987

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ABSTRACT

Purpose
The combination of gemcitabine plus cisplatin (GC) is a standard regimen in patients with locally advanced or metastatic urothelial cancer. A phase I/II study suggested that a three-drug regimen that included paclitaxel had greater antitumor activity and might improve survival.

Patients and Methods
We conducted a randomized phase III study to compare paclitaxel/cisplatin/gemcitabine (PCG) with GC in patients with locally advanced or metastatic urothelial carcinoma. Primary outcome was overall survival (OS). Secondary outcomes were progression-free survival (PFS), overall response rate, and toxicity.

Results
From 2001 to 2004, 626 patients were randomly assigned; 312 patients were assigned to PCG, and 314 patients were assigned to GC. After a median follow-up of 4.6 years, the median OS was 15.8 months on PCG versus 12.7 months on GC (hazard ratio [HR], 0.85; $P = .075$). OS in the subgroup of all eligible patients was significantly longer on PCG (3.2 months; HR, 0.82; $P = .03$), as was the case in patients with bladder primary tumors. PFS was not significantly longer on PCG (HR, 0.87; $P = .11$). Overall response rate was 55.5% on PCG and 43.6% on GC ($P = .0031$). Both treatments were well tolerated, with more thrombocytopenia and bleeding on GC than PCG (11.4% *v* 6.8%, respectively; $P = .05$) and more febrile neutropenia on PCG than GC (13.2% *v* 4.3%, respectively; $P < .001$).

Conclusion
The addition of paclitaxel to GC provides a higher response rate and a 3.1-month survival benefit that did not reach statistical significance. Novel approaches will be required to obtain major improvements in survival of incurable urothelial cancer.

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INTRODUCTION

Untreated metastatic urothelial carcinoma is associated with a median survival time rarely exceeding 3 to 6 months. It is a chemotherapy-sensitive tumor, and cisplatin-based chemotherapy is the standard treatment.[1,2] Historically, the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) modestly improved survival compared with cisplatin alone[3]; the combination of cyclophosphamide, doxorubicin, and cisplatin[4]; and a carboplatin-based regimen.[5] However, dose intensification of MVAC did not improve median survival,[6-8] and the disappointing long-term outcome with available regimens has led to the search for new active drugs.

Among the agents assessed, the microtubule-stabilizing taxane paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) and the pyrimidine antimetabolite gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) have demonstrated high single-agent activity in patients with advanced urothelial cancer. In previously untreated patients, paclitaxel produced a response rate of 42%, with a 27% complete response rate.[9] Gemcitabine has single-agent activity against urothelial cancer in previously treated

and untreated patients, with overall response rates in the range of 24% to 28%.[10-13]

The encouraging results with gemcitabine led to a phase III trial comparing a combination of gemcitabine and cisplatin (GC) with MVAC.[2] GC provided a similar survival compared with MVAC with a better safety profile and tolerability. This favorable risk-benefit ratio established GC as another standard option for patients with locally advanced and metastatic transitional-cell carcinoma.

Given the different mechanisms of action and the partially nonoverlapping toxicity profiles of cisplatin, gemcitabine, and paclitaxel, the triple combination was assessed by the Spanish Oncology Genitourinary Group.[14,15] In 58 patients with advanced urothelial tumors in the combined phase I/II cohort, the overall response rate was 77.6% (95% CI, 60% to 98%). There were 16 complete responses (27.6%), and the median survival time was 15.6 months.[14,15] Thus, the three-drug combination was feasible, and the median survival seemed superior to that obtained with the standard MVAC regimen.[2] Therefore, the European Organisation for Research and Treatment of Cancer (EORTC) designed a phase III study (EORTC Intergroup Study 30987) to compare the efficacy of GC plus paclitaxel (PCG) with GC alone in patients with locally advanced or metastatic urothelial cancer. Preliminary data from this study, with a median follow-up of 3.4 years, were presented at the 43rd Annual Meeting of the American Society of Clinical Oncology in 2007[16]; this article presents the final mature results after a median follow-up of 4.6 years.

PATIENTS AND METHODS

Design

An open-label randomized, phase III intergroup study was conducted within the framework of the EORTC Genitourinary Group, with the cooperation of the German Association of Urologic Oncology, Groupe d'Etude des Tumeurs Uro-Génitales, National Cancer Institute of Canada Clinical Trials Group, Spanish Oncology Genitourinary Group, Southwest Oncology Group, and the National Cancer Research Institute Bladder Clinical Studies Group.

Eligibility

Eligible patients had histologically confirmed stage IV locally advanced (T4b, any N; or any T, N2-3) or metastatic transitional-cell carcinoma of the urothelium (pure or mixed). Tumor sites included the bladder, urethra, ureter, and renal pelvis. Patients were required to have measurable or nonmeasurable (evaluable) disease according to RECIST,[17,18] age $\geq$ 18 years, WHO performance status of 0 or 1, and a life expectancy of at least 12 weeks. Patients who received prior systemic chemotherapy or investigational agents were not allowed to enter the study. Other inclusion criteria were adequate hematologic (WBC count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin $\geq$ 10 g/dL or 6.2 mmol/L), hepatic (serum bilirubin level $<$ 1.25$\times$ above the normal range, ALT or AST $<$ 2.5$\times$ above the normal range), and renal (creatinine clearance $\geq$ 60 mL/min) function. Patients with significant cardiac disease, brain metastases, or peripheral neuropathy greater than grade 2 were not eligible. Patients with a secondary primary malignancy, except for in situ carcinoma of the cervix, basal cell carcinoma of the skin, or incidental prostate cancer (T1, Gleason score $\leq$ 6, prostate-specific antigen $<$ 0.5 ng/mL), were also not eligible.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol was approved by the institutional review board of each participating center, and relevant patient safeguards were observed. All patients provided written informed consent.

Treatment Schedule

Patients were centrally randomly assigned at the EORTC to receive either PCG (experimental arm) or GC (control arm). Random assignment was stratified by study site, WHO performance status (0 *v* 1), and the presence or absence of metastatic disease. Treatment schedule and dose adjustments were done according to previously published data.[2] In summary, in the GC arm, gemcitabine 1,000 mg/m^2 was administered on days 1, 8, and 15, and cisplatin 70 mg/m^2 was administered on day 2, every 28 days. The PCG arm consisted of

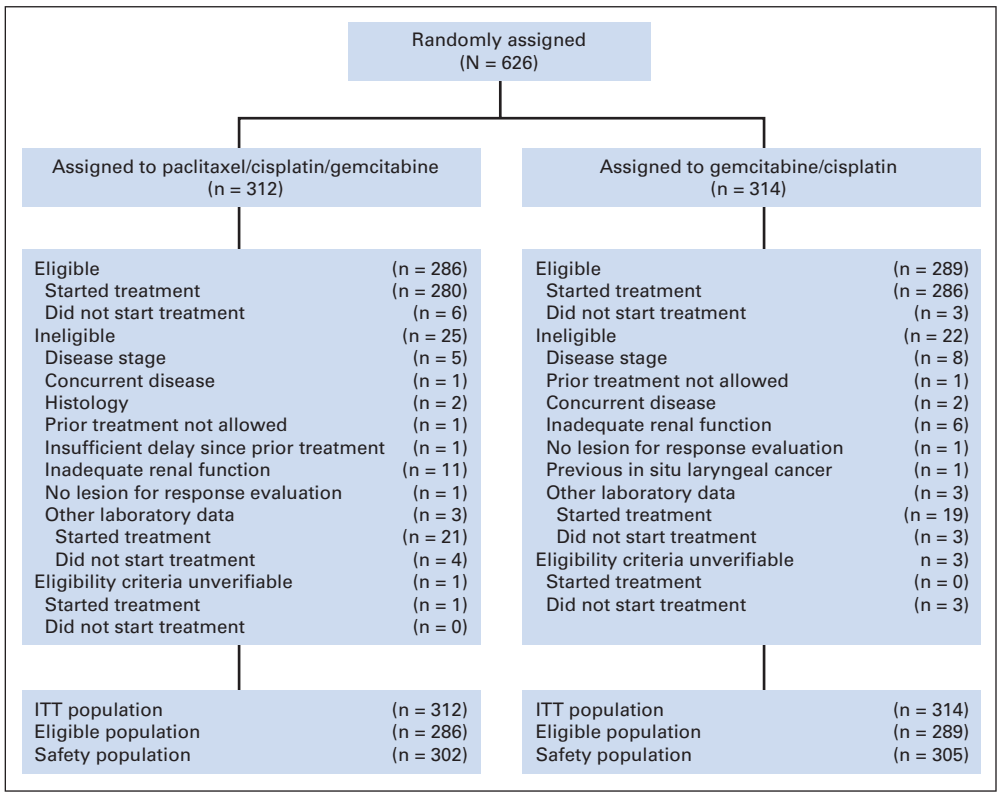

Fig 1. Flow chart of the study population. Eligibility before the database lock was assessed by the study coordinator (J.B.) and thereafter reviewed by the statisticians (R.S. and S.C.) and the clinical research physician (S.M.). ITT, intent to treat.

the sequential administration of paclitaxel 80 mg/m^2 before the same doses of gemcitabine and paclitaxel as in the GC arm on day 1. Paclitaxel and gemcitabine were administered at the same doses on day 8. Cycles were repeated every 21 days. Patients were treated for a maximum of six cycles or until documentation of progression according to RECIST,[17] unacceptable toxicity, or a request for discontinuation by the patient or attending physician.

Study End Points

The primary end point was overall survival (OS), which was defined as the time between random assignment and death from any cause. Secondary end points were progression-free survival, response rate according to RECIST,[17] and toxicity using the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0. Patients were assessable for response if they had evaluable disease (measurable and/or non measurable), had received at least one cycle, and had at least one follow-up tumor assessment. Response had to be confirmed after at least 4w. Patients were evaluated every 3m during the first 2y and every 6m thereafter.

Statistical Considerations

The median survival on GC was assumed to be 14 months. The trial was designed to detect an increase in the median survival from 14 months to 18 months on PCG (or equivalently an increase in the 14 month survival rate from 50% to 58.7%), which corresponds to a hazard ratio (HR) of 0.778. It was estimated that a total of 610 patients (305 patients in each arm) was needed to observe the 498 deaths required based on a two-sided log-rank test at error rates of $\alpha = .05$ and $\beta = .20$. Two interim efficacy analyses were carried out in January 2004 and June 2007. To maintain the overall α at 5%, the significance level used for the final analysis was 3.9%.

The primary analysis was carried out in the intent-to-treat (ITT) population of all randomly assigned patients. Time-to-event curves (duration of OS and PFS) were estimated using the Kaplan-Meier method and compared based on a two-sided log-rank test. Response rates were compared using a χ^2 test. Survival was also compared in the eligible patients (unplanned, post hoc analysis).

RESULTS

Between May 2001 and June 2004, 626 patients from 137 institutions were randomly assigned, 314 patients to GC and 312 patients to PCG. The 607 patients who started treatment were included in the safety analyses. Forty-seven patients (22 patients on GC and 25 patients on PCG) were ineligible, with an additional four patients with eligibility unverifiable, 41 of whom started protocol treatment (Fig 1).

Patient Characteristics

Patient characteristics at random assignment were well balanced between the arms. Baseline data are listed in Table 1.

Table 1. Patient Demographics and Disease Characteristics at Random Assignment

Demographic or Characteristic	Paclitaxel/ Cisplatin/ Gemcitabine (n = 312)		Gemcitabine/ Cisplatin (n = 314)		Total (N = 626)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex						
Male	256	82.3	252	81.0	508	81.7
Female	55	17.7	59	19.0	114	18.3
Age, years						
Median	61		61		61	
Range	27-80		32-79		27-80	
WHO performance status						
0	171	54.8	171	54.5	342	54.6
1	141	45.2	143	45.5	453	45.5
Location of primary tumor						
Bladder	254	81.4	259	82.5	513	81.9
Renal pelvis	27	8.6	25	8.0	52	8.3
Ureter	13	4.2	17	5.4	30	4.8
Urethra	11	3.5	8	2.5	19	3.0
Other	6*	1.9	2†	0.6	8	1.3
Distant metastases	275	88.1	276	87.9	551	88.0
Nonvisceral metastases	130	41.7	121	38.5	251	40.1
Visceral metastases‡	145	46.5	155	49.4	300	47.9
Bone	51	16.3	57	18.2	108	17.3
Liver	41	13.1	51	16.2	92	14.7
Lung	70	22.4	84	26.8	154	24.6
Peritoneum	19	6.1	12	3.8	31	5.0
No. of metastatic sites						
1	108	34.6	110	35.0	218	34.8
2	86	27.6	89	28.3	175	28.0
≥ 3	81	26.0	77	24.5	158	25.2
Prognostic risk group§						
Low	98	31.4	93	29.6	191	30.5
Intermediate	136	43.6	135	43.0	271	43.3
High	77	24.7	83	26.4	160	25.6

Abbreviations: GC, gemcitabine + cisplatin; PCG, paclitaxel/cisplatin/gemcitabine.
*One patient missing data.
†Three patients missing data.
‡CNS: 1 patient on PCG and 0 on GC; bone marrow: 0 patients on PCG and 2 on GC.
§Based on Bajorin et al.[19]

Survival

After a median follow-up of 4.6 years (maximum, 6.8 years), 504 patients (80.5%) have died, 256 (81.5%) on GC and 248 (79.5%) on PCG. Causes of death were urothelial cancer in 434 patients (226 patients [72%] on GC and 208 patients [66.7%] on PCG), toxicity in nine patients, chronic disease in one patient, other causes in 36 patients, and unknown in 24 patients.

The median OS was 3.1 months longer in the PCG arm; median OS was 15.8 months (95% CI, 13.6 to 17.5 months) on PCG compared with 12.7 months (95% CI, 11.0 to 14.4 months) on GC. However, the difference in median OS did not reach statistical significance (HR, 0.85; 95% CI, 0.72 to 1.02; $P = .075$; Fig 2). The OS rates at 1 and 4 years were 61.4% (95% CI, 55.7% to 66.6%) and 17.2% (95% CI, 13.0% to 21.8%), respectively, on PCG, compared with 52.8% (95% CI, 47.0% to 58.2%) and 16.4% (95% CI, 12.3% to 20.9%), respectively on CG. Results were similar when adjusted simultaneously by cooperative group, WHO performance status, and presence or absence of metastatic disease.

All eligibility criteria including laboratory values were checked according to the most recent information available at the time of random assignment. Forty-seven patients (8%) were ineligible, mostly for reasons of disease stage and/or impaired renal function. Ten of these patients did not start the allocated treatment or were not physically fit enough to receive optimal treatment. Hence, we also analyzed OS in the eligible patient population, which showed that patients treated with the triplet had a significantly longer duration of survival (median, 15.9 months; 95% CI, 13.6 to 18.1 months) than patients in the GC arm (median, 12.7 months; 95% CI, 11.4 to 14.4 months; HR, 0.82; 95% CI, 0.68 to 0.98; $P = .03$; Fig 3).

After recent reports that outcome in tumors of the upper urinary tract may differ from outcome in tumors of the lower tract,[20] the

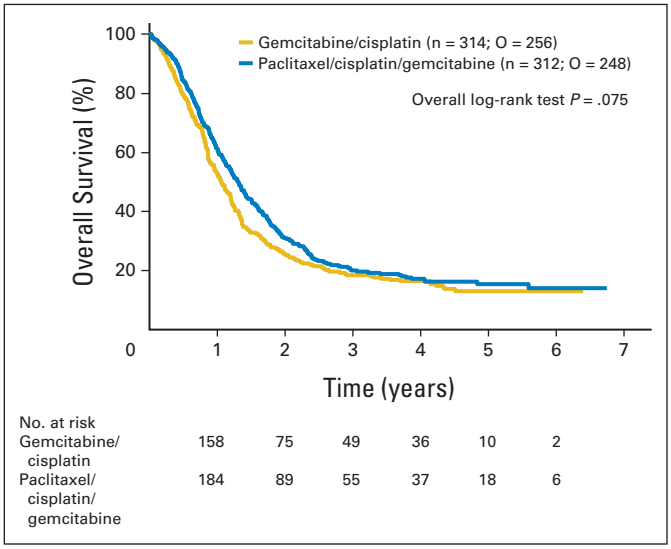

Fig 2. Overall duration of survival in the intent-to-treat patient population. O, number of observed events.

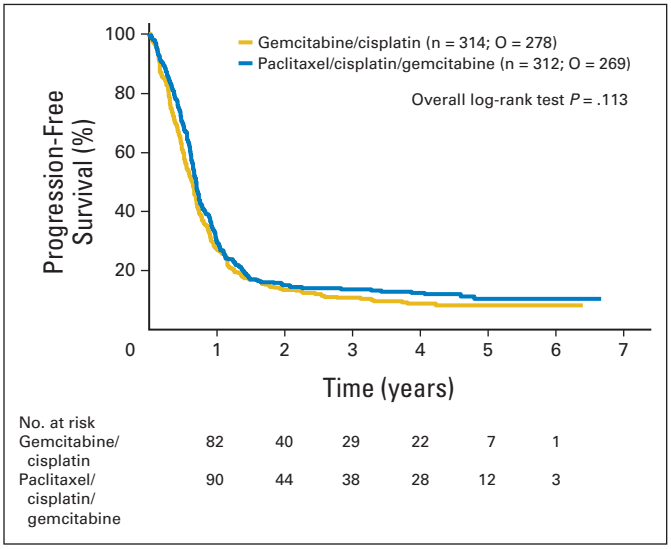

Fig 4. Duration of progression-free survival. O, number of observed events.

possible influence of anatomic site on treatment effect was investigated in an analysis that was not preplanned. Among the 81% of patients in whom the bladder was the site of the primary tumor, median OS after PCG was significantly longer than that after GC (15.9 *v* 11.9 months, respectively; HR, 0.80; 95% CI, 0.66 to 0.97; $P = .025$).

Prognostic factor analyses in the ITT population, independent of the treatment administered, showed statistically significant differences in survival according to WHO performance status (1 *v* 0: HR, 1.50; 95% CI, 1.26 to 1.79; $P < .001$), metastatic disease (presence *v* absence: HR, 1.38; 95% CI, 1.13 to 1.69; $P = .001$), visceral metastases (presence *v* absence; HR, 1.74; 95% CI, 1.46 to 2.08; $P < .001$), and number of Memorial Sloan-Kettering Cancer Center risk factors (two risk factors *v* no or one risk factor: HR, 2.17; 95% CI, 1.79 to 2.64; $P < .001$).

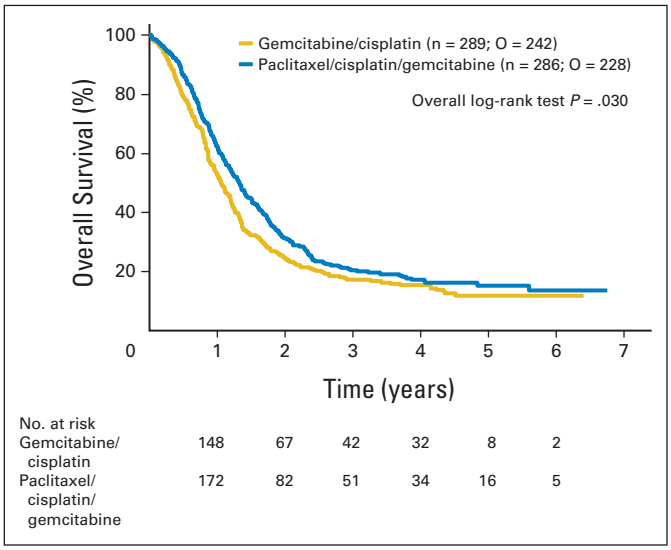

Fig 3. Overall duration of survival in the eligible patients. O, number of observed events.

PFS

Progression or death was documented in 547 patients, 278 on GC and 269 on PCG. The median PFS was 8.3 months on PCG and 7.6 months on GC (HR, 0.87; 95% CI, 0.74 to 1.03; $P = .113$; Fig 4).

Response Rate

The overall response rate (complete or partial; blinded review by J.B.) was significantly higher among patients treated with PCG than GC (55.5% *v* 43.6%, respectively; $P = .0031$). Response to treatment is shown in Table 2. Overall, 48 patients (21 patients in the PCG arm and 27 patients in the GC arm) underwent postchemotherapy surgical resection.

Drug Exposure and Toxicity

Of the 626 randomly assigned patients, 607 started the protocol treatment, 302 on PCG and 305 on GC (three patients refused, three patients had disease progression before start, four patients had other complicating diseases, four patients had other reasons, and information was lacking in five patients). The median duration of treatment

Table 2. Overall Response According to RECIST

Best Overall Response to Treatment	Paclitaxel/ Cisplatin/ Gemcitabine (n = 312)		Gemcitabine/ Cisplatin (n = 314)		Total (N = 626)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Complete response	42	13.5	35	11.1	77	12.3
Partial response	131	42.0	102	32.5	233	37.2
Stable disease	69	22.1	97	30.9	166	26.5
Progression of disease	21	6.7	47	15.0	68	10.9
Early death	8	2.6	7	2.2	15	2.4
Not assessable	31	9.9	17	5.4	48	7.7
Treatment never started	10	3.2	9	2.9	19	3.0

Table 3. Nonhematologic and Hematologic Adverse Events

Adverse Event	Gemcitabine/Cisplatin (n = 305)				Paclitaxel/Cisplatin/Gemcitabine (n = 302)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Nonhematologic adverse events								
Vomiting	19	6.2	1	0.3	20	6.6	1	0.3
Pulmonary toxicity	12	3.9	3	1.0	12	4.0	4	1.3
Cardiovascular events*	36	11.8	7	2.3	28	9.3	5	1.6
Allergy	0	0	1	0.3	5	1.7	4	1.3
Fatigue	34	11.1	0		43	14.2	4	1.3
Bleeding	22	7.0	1	0.3	9	2.9	1	0.3
Infection	40	13.1	4	1.3	49	16.2	8	2.6
Renal toxicity	10	3.3	5	1.6	11	3.6	3	1.0
Neuropathy/sensory	1	0.3	0	0	0	0	1	0.3
Alopecia	2	0.7	0	0	5	1.7	0	0
Diarrhea	10	3.3	1	0.3	14	4.6	0	0
Hematologic adverse events								
WBC	102	33.4	16	5.2	102	33.8	53	17.5
Neutropenia	93	30.5	61	20.0	86	28.5	108	35.8
Thrombocytopenia	140	45.9	19	6.2	92	30.5	12	4.0
Hemoglobin	70	23.0	8	2.6	60	19.9	8	2.6

*Includes edema, hypotension, thrombosis/embolism, and other cardiovascular events.

was 16.3 weeks (range, 0.1 to 219 weeks). Appendix Table A1 (online only) lists treatment duration, dose reduction, and discontinuation.

Overall, the addition of paclitaxel to the combination of GC had little effect on the frequency or severity of toxic effects. Details of nonhematologic and hematologic adverse events are listed in Table 3.

Patients on the PCG arm, compared with patients on the GC arm, experienced more grade 4 neutropenia (35.8% *v* 20%, respectively; $P < .001$), more febrile neutropenia (13.2% *v* 4.3%, respectively; $P < .001$), and a greater need for granulocyte colony-stimulating factor administration (17% *v* 11%, respectively; $P = .03$). However, there was no difference between treatments in the occurrence of neutropenic sepsis. Grade 4 thrombocytopenia was more frequent in the GC arm versus the PCG arm (6.2% *v* 4.0%, respectively; $P = .03$). Grade 3 or 4 thrombocytopenia associated with grade 3 bleeding was also more frequent in the GC arm than the PCG arm (11.4% *v* 6.8%, respectively; $P = .05$).

Severe acute toxicity (toxic death, grade 3 or 4 thrombocytopenia with grade 3 or 4 hemorrhage, grade 4 thrombocytopenia with hemorrhage, grade 3 asthenia at first cycle, grade 4 asthenia during treatment, grade 3 or 4 renal toxicity, grade 3 or 4 neutropenic fever, or grade 3 or 4 mucositis) was observed in 20.2% of patients on PCG (including six toxic deaths) and in 14.8% of patients on GC (including three toxic deaths).

DISCUSSION

This large, multinational, intergroup, phase III study, to our knowledge the largest study ever conducted in locally advanced or metastatic urothelial carcinoma, enrolling more than 600 patients over 3 years, confirms that cooperative groups on two continents can work together to provide timely answers to important clinical questions in this disease. The study shows that the three-drug combination of PCG provides a better response rate and a 3.1-month prolongation in median survival when compared with standard GC alone. The 15.8-month median OS on the triplet in this trial closely matches the outcome in the phase II study.[14,15] The present findings also confirm the tolerability of the PCG regimen.

The trial was designed to detect a difference of 4 months in median survival between GC and PCG. The choice of 4 months was driven by the expected median survival of 18 months initially obtained in the phase I/II dose-finding study.[15] The phase III study reported here showed a difference of 3.1 months in the OS in the ITT population, which is a strong trend but did not reach statistical significance. In view of the potential dilution effect of 8% ineligible patients, some of whom either did not receive the allocated treatment or were not physically fit enough to receive optimal treatment, we also carried out an analysis in the 575 eligible patients, which showed a median survival advantage of 3.2 months favoring the triplet compared with GC (15.93 *v* 12.71 months, respectively) and a reduction of 18% in the risk of death (HR, 0.82), which did reach statistical significance ($P = .030$). The eligibility was assessed based on measurements taken before random assignment so exclusion of the ineligible patients does not bias the treatment comparison, even though this has the limitation of being an additional unplanned analysis. The planned requisite of a 4-month difference in the median duration of survival based on those data was highly ambitious.[15] The fact that the effect sought in the ITT patient population was not attained cannot be attributed to prerandomization differences in prognostic factors between the treatment groups because the two arms were generally well balanced regarding performance status and visceral metastases. This was further demonstrated in the ITT population because the conclusions were not affected after adjusting for these variables.

In addition, the trial has raised an intriguing issue of wide clinical importance. In a post hoc analysis, there was evidence of a greater and

statistically significant survival benefit in patients with bladder primaries receiving the triple regimen (median, 15.9 months for PCG *v* 11.9 months for GC) in contrast to patients with nonbladder primaries, in whom there was no benefit. Pathologic findings in large series of upper tract urothelial cancer reveal that these tumors tend to have higher grade and stage than bladder cancer.[20] Despite morphologic similarities, there are genetic and epigenetic differences between transitional-cell carcinoma in the upper and lower urinary tracts. First, embryologically, the urothelium of bladder and ureter arises from different tissues.[21] Second, in vitro studies have shown that urothelium from the two sites differs in uroplakin content, keratin expression pattern, growth potential, and propensity to keratinize.[22] Extracellular matrix–associated proteins with counter-adhesive properties respond differently in ureteric and bladder urothelial cells.[23] Mono- and dinucleotide microsatellite instability, a feature of tumors with deficient mismatch repair, is more common in upper than lower urinary tract cancers,[24,25] and these tumors have more extensive methylation than bladder cancers.[26] To our knowledge, this study is the first to show a trend in OS advantage in a subgroup of patients with advanced urothelial cancer with bladder being the primary origin. The fact that the benefit by the triplet seems to be obtained particularly in bladder urothelial cancer and that upper tract urothelial cancer may be less responsive to chemotherapy implies that patients with bladder primaries (by far the most common site of urothelial cancer) should perhaps be treated differently from patients with urothelial tumors arising at other sites. Consequently, in the future, trials will need to prospectively analyze this hypothesis in addition to testing the importance of methylating patterns and other molecular factors.

Finally, the present results are consistent with previous findings and confirm that the GC schedule as studied in the randomized phase III study of GC versus MVAC[2] may be more toxic in terms of grade 4 thrombocytopenia than most clinicians expect, often resulting in the need for omission of gemcitabine on day 15. Newer regimens with GC using a 21-day schedule are being developed to reduce the need to administer gemcitabine on day 15, which often requires adjustment because of high hematologic toxicity.

The modest survival benefit for the combination of PCG observed in this report has been shown in an exploratory analysis in the eligible patients. The eligible patient population corresponds to the population targeted by the protocol and to whom the results are to be generalized, and therefore, this might be considered to be a more meaningful analysis. In the future, to select patients most likely to benefit from the triple therapy, the development of biomarkers that predict outcome or sensitivity to chemotherapy is an essential first step. Pharmacogenomics and genomics might eventually play a role in the selection of better candidates for treatment and aid in the personalized design of treatment.

In conclusion, this large, multinational, phase III trial in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy shows that the triple combination of PCG provides a higher response rate when compared with GC. The predefined primary end point for OS improvement was not reached in the overall patient population, but the 3.2-month survival difference in the population of all eligible patients reached statistical significance. Moreover, a benefit in patients with a bladder primary was also observed in an analysis that was not preplanned. Finally, the triple combination was not appreciably more toxic than the GC regimen in this population. Ongoing studies may assist to identify patients who will derive the most benefit of taxane-based triple chemotherapy. Novel strategies will be required to have a major impact on survival in this disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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