Cisplatin and Gemcitabine With Either Vinorelbine or Paclitaxel in the Treatment of Carcinomas of Unknown Primary Site

Results of an Italian Multicenter, Randomized, Phase II Study

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BACKGROUND. To date, the standard treatment for patients who have carcinoma of unknown primary site has not been established.

METHODS. In this randomized Phase II study, 66 previously untreated patients (33 patients per arm) with carcinomas of unknown primary site received cisplatin (35 mg/m^2) and gemcitabine (1000 mg/m^2) with either paclitaxel (70 mg/m^2) or vinorelbine (25 mg/m^2), and all drugs were administered intravenously on Days 1 and 8 of a 21-day cycle. Twenty-nine patients (44%) presented with ≥ 2 involved sites. The pathologic diagnosis was mainly adenocarcinoma (48 patients; 72.7%) and squamous carcinoma (7 patients; 10.6%).

RESULTS. In the first arm, 16 patients (48.5%) experienced an objective response, and 9 patients (27.2%) had disease stabilization. In the vinorelbine-containing arm, 14 patients (42.3%) experienced an objective response, and 8 patients (24.2%) had disease stabilization. The median response duration and the median time to progression were similar in both treatment arms; the median overall survival was 9.6 months (95% confidence interval, 7.11–12.09 months) for patients who received the cisplatin/gemcitabine/paclitaxel regimen and 13.6 months (95% confidence interval, 6.61–20.59 months) for patients who received the vinorelbine combination. Grade 3 and 4 toxicities were more frequent in the paclitaxel-containing arm.

CONCLUSIONS. Both combinations satisfied the 2-step design, demonstrating antitumor activity without relevant differences in response rates or response duration; however, the vinorelbine-containing regimen yielded superior results both in terms of overall survival (13.6 months vs 9.6 months) and in terms of treatment tolerability. Therefore, according to a *pick the winner* attitude, the combination of cisplatin/gemcitabine/vinorelbine may be considered in the design of future randomized, Phase III trials for patients with carcinomas of unknown primary site. *Cancer* **2006;107:2898–905.** © *2006 American Cancer Society.*

KEYWORDS: carcinoma, unknown primary, chemotherapy, cisplatin, gemcitabine, vinorelbine, paclitaxel.

Carcinomas of unknown primary site (CUP) represent a distinct but heterogeneous group of metastatic tumors, accounting for 2.3% to 4.2% of all cancers[1] in which the primary site of origin cannot be detected during pretreatment evaluation.[2] Despite significant improvement in many diagnostic techniques, eg, tumor imaging and pathologic evaluation of tissue samples, CUP represents an extremely challenging clinical entity in terms of treatment. Indeed, the real impact of chemotherapy on the natural history of CUP remains to be determined, and the median survival of patients with CUP rarely exceeds 12 months.[3] Although cisplatin-based regimens have yielded better response rates (usually in the range from 23% to 39%), median survival results remain unsatisfactory, ranging from 5 months to 9 months,[4] and no standard treatment has been established to date.[5]

The recent availability of newer, broadly active chemotherapeutic agents (eg, gemcitabine, vinorelbine, and the taxanes, among others) has created new options in the therapeutic strategy for patients with CUP. Here, we report the results of a multicenter, randomized, Phase II trial evaluating the efficacy and toxicity profile of the combination of cisplatin (Pfizer Pharmaceuticals, New York, NY) and gemcitabine (Eli-Lilly, Indianapolis, IN) combined either with vinorelbine (PierreFabre Medicament, Castres Cedex, France) or with paclitaxel (Bristol-Myers Squibb, Princeton, NJ) for the treatment of CUP.

MATERIALS AND METHODS
Diagnostic Workup
Patients with histologically (or cytologically) documented, metastatic carcinoma were considered eligible for the current study when the following diagnostic procedures did not allow a primary origin to be identified: complete history and thorough physical examination, blood chemistry (including, in men, serum tumor marker for prostate-specific antigen [PSA], α-fetoprotein, and β-human chorionic gonadotropin), urinalysis, mammography in women, thoracic and abdominopelvic computed tomography scans, bone scan, and symptom- or sign-oriented imaging or endoscopic studies. Patients were enrolled if light microscopic pathologic analysis showed a well or poorly differentiated adenocarcinoma, a poorly differentiated carcinoma, or any squamous cell carcinomas. Specific pathologic analyses were mandatory to rule out lymphomas (ie, staining for leukocyte common antigen), malignant melanoma (ie, staining for both S100 and HMB45), extragonadal germ cell neoplasms (ie, staining for both α-fetoprotein and β-human chorionic gonadotropin), sarcomas (ie. staining for cytokeratins and vimentin), neuroendocrine

tumors (ie, staining for chromogranin and synaptophysin), and prostatic adenocarcinomas in men (ie, staining for PSA).

PATIENTS
Along with a histologically (or cytologically) confirmed diagnosis of CUP, eligibility criteria included measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, age between ≥ 18 years and ≤ 75 years, a life expectancy ≥ 12 weeks, and written informed consent obtained according to the institutional requirements.

Patients also were required to have adequate organ function, which was defined by the following parameters: white blood cells $\geq 3000/\mu L$, platelets $\geq 100,000/\mu L$, hemoglobin ≥ 9.5 g/dL, bilirubin < 1.5 mg/dL, aspartate and alanine aminotransferase levels < 3 times the upper limit of normal, and creatinine < 2.0 mg/dL. The presence of significant comorbidities, including uncontrolled diabetes, active systemic infections, a history of severe coronary artery disease or myocardial infarction within the last 6 months, psychiatric conditions, the presence of central nervous system metastases, a history of other cancers within the previous 5 years (except localized non-melanomatous skin cancer or well-managed in situ uterine carcinoma), and pregnancy or lactation, were considered exclusion criteria. Patient subgroups that were suitable for well-defined treatments (ie, women with adenocarcinoma involving axillary lymph nodes as the only site of disease, women with papillary serous carcinoma of the peritoneum, patients with squamous cell carcinoma that involved either cervical or inguinal lymph nodes only, patients with poorly differentiated carcinomas that suggested germinal tumors and with elevated levels of β-human chorionic gonadotropin and/or α-fetoprotein, and patients with carcinoma that involved a single, potentially resectable site) also were excluded from enrolment.

Treatment Schedule
In the first treatment arm (cisplatin, gemcitabine and vinorelbine [CGV]), vinorelbine (25 mg/m^2) was added to a cisplatin (35 mg/m^2) and gemcitabine (1000 mg/m^2) combination and all drugs were administered intravenously on Days 1 and 8 of a 21-day cycle. Gemcitabine was administered over 30 minutes before cisplatin.

In the second treatment arm (cisplatin, gemcitabine, and paclitaxel [CGT]), paclitaxel (70 mg/m^2) given as a 1-hour intravenous infusion, replaced the vinorelbine. Cisplatin and gemcitabine were delivered as specified above for the CGV arm.

In the CGT arm, all patients received premedication with steroids and antihistamine drugs according

to the practice of each center. Antiemetic treatment was provided at each researcher's discretion.

A minimum of 3 cycles was required before the first tumor response assessment; then, a complete reevaluation was performed every 3 cycles of chemotherapy employing the same staging procedures that identified the metastatic sites of disease at baseline. The study treatments were administered mainly on an outpatient basis.

Assessment of Response and Toxicity

Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were assessed according to World Health Organization criteria.[6] A CR was defined as complete regression of all lesions and signs and symptoms of disease. A PR was defined as a reduction ≥50% in the sum of the product of the 2 greatest dimensions of all measurable lesions, including partial healing of lytic lesions or reduction in the number of the uptake areas, that lasted ≥2 months. SD was considered a reduction <50% or an increase <25% in the sum of the product of the same 2 greatest dimensions of measurable lesions that lasted ≥3 months. PD was defined as an increase >25% in the sum of the product of the 2 greatest dimensions of all measurable lesions and/or the appearance of new lesions. Chemotherapy-related toxic effects were recorded according to the National Cancer Institute's Common Toxicity Criteria, version 3.0,[7] at every cycle and at the end of treatment.

Statistical Considerations

The primary endpoint of this randomized Phase II study was the evaluation of the overall response rate (ORR); secondary objectives were the analysis of the toxicity profile, the time to progression (TTP), the duration of response, the overall survival (OS) for the 2 treatment arms, the correlation between disease characteristics (extension, sites of disease, etc), and clinical and/or pathologic parameters. A noncomparative analysis of these parameters in both treatment arms was performed to select the best regimen according to a *pick the winner* attitude. For this randomized Phase II study, the sample size was calculated by applying a Simon 2-step minimax design.[8]

Considering a 40% ORR clinically important with a type-1 error of 5% and a type-2 error of 20%, 18 patients in each treatment arm were required for initial treatment. If ≥5 of the first 18 patients obtained an objective response, then accrual would continue until the final enrolment of a total of 33 patients per arm. The TTP was calculated the date chemotherapy was started until there was clinical and/or radiologic evidence of PD; OS was calculated from the date chemotherapy was started until the date of death or last documented follow-up. All data concerning TTP and OS were analyzed according to the Kaplan-Meier method[9] by using the SPSS statistical software package. Finally, to determine whether some clinical parameters (patient age, ECOG PS and the number of metastatic sites) could be identified as prognostic factors, their possible impact on response rate and survival was evaluated by performing a multivariate analysis with a logistic regression model and a Spearman correlation model, respectively.

RESULTS

Patient Characteristics

From March 2001 to August 2003, 66 chemotherapy-naive patients were assigned using blocked randomization to both treatment arms (33 patients in each arm). Written informed consent was obtained from all enrolled patients. All patients were assessable for response and toxicity.

Patients' baseline characteristics, which were well balanced between the 2 treatment arms, are summarized in Table 1. Fifty-two patients were men (78.8%), 14 patients were women (21.2%), and the median patient age was 60.5 years. The ECOG PS was 0 in 22 patients (33.3%), 1 in 42 patients (63.6%), and 2 in the remaining 2 patients (3%).

Twenty-nine of 66 patients (43.9%) presented with ≥2 metastatic sites, with lymph nodes the most frequent disease localization (82%), followed by bone (27.3%) and liver (27.3%). Histologic types were adenocarcinoma in 48 patients (72.7%), squamous cell in 7 patients (10.6%), anaplastic in 5 patients (7.6%), epithelioid in 5 patients (7.6%) and medullary in 1 patient (1.5%).

Response

In total, 297 cycles (155 cycles in the CGT arm; 142 cycles in the CGV arm) were administered with a median of 4 cycles of treatment per patient in the vinorelbine-containing arm and 5 cycles per patient in the paclitaxel-containing arm. According to the research protocol, we proceeded to the second step of the study after obtaining 5 objective responses in the first 18 patients in each treatment arm. In the CGT arm, 16 patients achieved an objective response (48.5%), 1 patient achieved a CR (3%) and 15 patients achieved a PR (45.5%); in the CGV arm, the ORR was 42.3%, and there were 3 CRs (9%) and 11 PRs (33.3%).

Nine patients in the CGT arm and 8 patients in the CGV arm had SD as their best response (27.3% and 24.2%, respectively), whereas PD occurred in 8 patients (24.2%) in the CGT arm and in 11 patients

TABLE 1
Patient Characteristics

	No. of patients (%)		
Characteristic	Total	CGT	CGV
Total enrolled	66 (100)	33 (50)	33 (50)
Assessable for activity	66 (100)	33 (50)	33 (50)
Assessable for toxicity	66 (100)	33 (50)	33 (50)
Age, y			
Median	60.5	60	61
Range	31–75	33–75	31–75
Sex			
Men	52 (78.8)	25 (75.5)	27 (81.8)
Women	14 (21.2)	8 (24.3)	6 (18.2)
ECOG PS			
0	22 (33.3)	10. (30.3)	12 (36.4)
1	42 (63.6)	22 (66.7)	20 (60.6)
2	2 (3)	1 (3)	1 (3)
Metastatic sites			
1	37 (56)	19 (57.6)	18 (54)
2	16 (24)	8 (24)	8 (24)
≥3	13 (20)	6 (18.2)	7 (21)
Site of disease			
Lung	16 (24)	6 (18.2)	10 (30)
Lymph nodes	54 (82)	29 (87.9)	25 (75.7)
Bone	18 (27.3)	7 (21)	11 (33.3)
Liver	18 (27.3)	8 (24)	10 (30.3)
Pleura	6 (9.1)	3 (9.1)	3 (9.1)
Skin	1 (1.5)	1 (3)	0
Pancreas	3 (4.5)	3 (9.1)	0
Other	8 (12.1)	3 (9.1)	5 (15)
Histologic type			
Adenocarcinoma	48 (72.7)	25 (75.7)	23 (73)
Anaplastic carcinoma	5 (7.5)	3 (9.1)	2 (6.1)
Squamous cell carcinoma	7 (10.6)	4 (12)	3 (9.1)
Medullary carcinoma	1 (1.5)	0	1 (3)
Epithelioid carcinoma	5 (7.6)	1 (3)	4 (12)

C indicates cis-diamminedichloroplatinum; G, gemcitabine; T, paclitaxel; V, vinorelbine; ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE 2
Response

	No. of patients (%)		
Response (N = 66 assessable patients)	CGT	CGV	Overall patient population
CR	1 (3)	3 (9)	4 (6)
PR	15 (45.5)	11 (33.3)	26 (39.4)
SD	9 (27.3)	8 (24.2)	17 (25.8)
PD	8 (24.2)	11 (33.3)	19 (28.8)

C indicates cis-diamminedichloroplatinum; G, gemcitabine; T, paclitaxel; V, vinorelbine, CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

FIGURE 1. Kaplan-Meier estimates of overall survival. VNR indicates vinorelbine; TXL, paclitaxel.
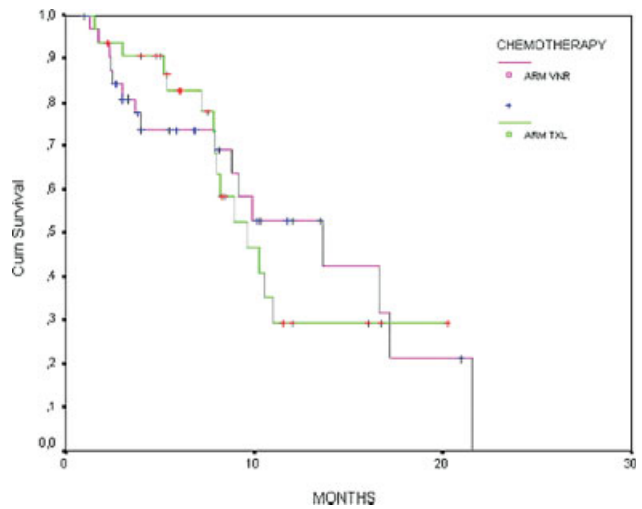
(33.3%) in the CGV arm (Table 2). The median response duration was similar in the 2 treatment arms: 7.5 months (95% confidence interval [95% CI], 5.6–9.4 months) in the CGV arm (mean, 10.28 months; range, 1–21.4 months) and 7.4 months (95% CI, 6.9–8.0 months) in the CGT arm (mean, 9 months; range, 2.2–16.7 months).

The median OS was 13.6 months (95% CI, 6.61–20.59 months; mean, 12.14 months; range, 1.03–21.5 months) for patients who received the CGV combination. For patients who received the CGT combination, the median OS was 9.6 months (95% CI, 7.11–12.09 months; mean, 10 months; range, 1.5–16.73 months). The median TTP also was similar in both treatments arms (6 months). The Kaplan-Meier curves for OS and TTP for each treatment arm are represented in Figures 1 and 2, respectively.

With reference to clinical parameters, such as prognostic factors, no correlation between the response rate and any clinical parameter was observed. However, there was a significant correlation between OS and PS (Spearman ρ, −0.263; 2-tailed $P < .05$), so that OS decreased with increasing PS.

Compliance With Treatment and Toxicity

The tolerability of the 2 treatment arms was acceptable. Overall, grade 3 and 4 toxicities were more frequent in the CGT arm, with 16 patients (48.5%) experiencing grade 3 or 4 adverse events versus 11 patients (33.3%) in the CGV arm. In the CGT arm, the most common hematologic toxicity was anemia, which occurred in 15 patients (45.5%) and was grade 3 or 4 in 3 patients (9.1%). In the CGV arm, the most common hematologic toxicity was neutropenia, which was experienced by 14 patients (42%) and was grade 3 or 4 in 4 patients (12%).
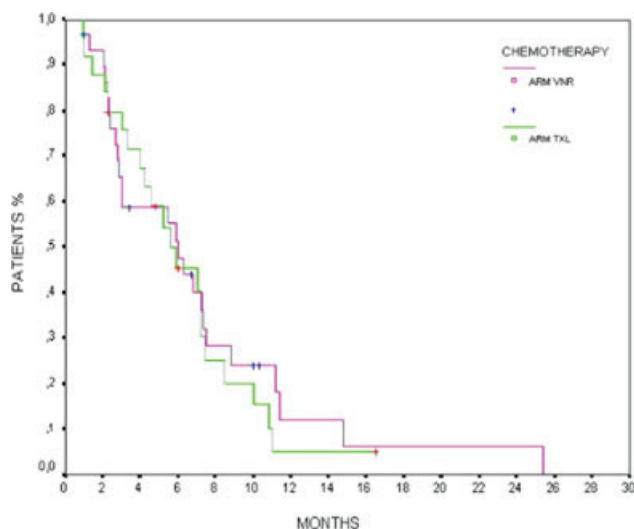
FIGURE 2. Kaplan-Meier estimates of time to progression. VNR indicates vinorelbine; TXL, paclitaxel.

TABLE 3
Hematologic Toxicity (Grades 3 and 4)

Toxicity (N = 66 assessable patients)	No. of patients (%)		
	CGT	CGV	Overall patient population
Neutropenia	6 (18.2)	4 (12)	10 (15)
Anemia	3 (9.1)	3 (9.1)*	6 (9)
Thrombocytopenia	4 (12)	3 (9.1)	7 (10.6)

C indicates cis-diamminedichloroplatinum; G, gemcitabine; T, paclitaxel; V, vinorelbine.
* Grade 3.

No febrile neutropenia was reported. Details about hematologic toxicity are reported in Table 3.

Among nonhematologic toxicities, episodes of nausea and emesis prevailed in both treatment arms (15 grade 1 or 2 episodes; 1 grade 3 or 4 episode), although they were more frequent in the CGT arm (8 grade 1 or 2 episodes; 1 grade 3 episode) than in the CGV arm (7 grade 1 or 2 episodes; 0 grade 3 or 4 episodes). Nonhematologic toxicities are reported in Table 4.

In the paclitaxel-containing arm, there was a single treatment withdrawal (caused by the onset of grade 3 cardiac toxicity), and there were 5 25%-dose reductions (2 caused by thrombocytopenia and 3 caused by renal toxicity, neutropenia, and nausea/emesis, respectively); whereas, in 2 other patients the scheduled dose for Day ≥8 was omitted (because of anemia and thrombocytopenia, respectively).

In the vinorelbine-containing arm, no treatment withdrawal was observed; whereas there were 7 25%-dose reductions (caused by thrombocytopenia, diarrhea, stomatitis, renal toxicity, neutropenia, nausea/

TABLE 4
Nonhematologic Toxicity (Grades 3 and 4)

Toxicity (N = 66 assessable patients)	No. of patients (%)		
	CGT	CGV	Overall patient population
Nausea/emesis	1 (3)*	0	1 (1.5)
Diarrhea	0	1 (3)*	1 (1.5)
Mucositis	1 (3)*	0	1 (1.5)
Neurotoxicity	0	0	0
Hepatotoxicity	0	0	0
Asthenia	0	0	0
Cardiotoxicity	1 (3)*	0	1 (1.5)
Nephrotoxicity	0	0	0

C indicates cis-diamminedichloroplatinum; G, gemcitabine; T, paclitaxel; V, vinorelbine.
* Grade 3.

emesis, and anemia in 1 patient each). In 9 patients, the scheduled dose for Day ≥8 was omitted (in 4 patients because of thrombocytopenia, in 3 patients because of neutropenia, and in 2 patients because of nausea/emesis and anemia).

DISCUSSION

CUPs constitute a heterogeneous and relatively rare group of malignancies. The survival of patients with CUP can vary mainly on the basis of histology, number and sites of disease, PS, and sex. For example, patients who present with neuroendocrine carcinoma or squamous cell carcinoma that infiltrates cervical lymph nodes who have <2 sites of disease, and lymph nodes as the only metastatic site, a good PS (<1) and who also are women are characterized by a more favorable prognosis. Conversely, adenocarcinomas and liver metastases are associated with poorer survival.[1,10]

The optimal first-line treatment for patients with CUP remains to be determined.[2,5] Previous trials of noncisplatin-based combinations, including 5-fluorouracil, cyclophosphamide, and doxorubicin, yielded disappointing results with response rates ranging from 10% to 33% and with median survival ranging from 4 months to 9 months.[11–17] Although cisplatin-based regimens have yielded better response rates (usually in the range of 23–39%), median survival results remain unsatisfactory, ranging from 5 months to 9 months.[14,15,17–19]

Until the 1990s, only 1 of 3 published Phase III, randomized trials in which a cisplatin-based regimen was compared with a noncisplatin-based regimen reported a survival advantage for patients who received cisplatin.[14,15,20] However, the suboptimal design of those Phase III studies, including small sample sizes

TABLE 5
Recent Phase II Studies in Patients with Cancer of Unknown Primary Origin (With Taxane- and Nontaxane-based Chemotherapy)

Author and year of publication	No. of patients	Regimen	Response rate (%)	Median survival (Months)
Briasoulis et al, 2000[21]	77	CbT	38.7	13
Greco et al, 2000[22]	71	CbET	48	11
Greco et al, 2000[23]	26	CDoc	26	8
	47 (Sequential)	CbDoc	22	8
Dowell et al, 2001[34]	34	CbE	19	8.4
		TFL	19	6.5
Greco et al, 2002[24]	120	CbGT	25	9
Balana et al, 2003[29]	30	CEG	36.6	7.2
Culine et al, 2003[30]	80	GC	55	8
		IC	38	6
Greco et al, 2004[25]	132	CbET GI	30	9.1
Pouessel et al, 2004[35]	36	DocG	40	10
Piga et al, 2004[31]	102	CbEA	26.5	9
Park et al, 2004[36]	37	TC	42	11
El-Rayes et al, 2005[37]	22	CbT	23	6.5
Schneider et al, 2005[38]	27	CbGCape	41	6.5
Huebner et al, 2005[32]	92	CT	21.6	10.7
		GV	21.4	6.9
Pittman et al, 2005[39]	50	GCb	30	8.1
Varadhachary et al 2005[40]	16 (5 2nd line)	GOx	36	NR
Palmeri et al (current study)	66	CGT	48.5	9.6
		CGV	42.3	13.6

Cb indicates carboplatin; T, paclitaxel; E, etoposide; C, cis-diamminedichloroplatinum; Doc, docetaxel; F, fluorouracil; L, leucovorin; G, gemcitabine; I, irinotecan; A, doxorubicin; Cape, capecitabine; Ox, oxaliplatin; NR, not reported; V, vinorelbine.

(55–95 patients), did not allow the authors to reach definitive conclusions about the role of cisplatin in the treatment of CUP.

Given the lack of randomized Phase III trials, it seemed necessary for us also to focus our attention on published Phase II studies. Indeed, Table 5 lists the more recent and/or important Phase II trials of different chemotherapy regimens in the treatment of CUP and includes the current study. It seems pertinent to remark here that, when reviewing the literature with clinical data based mainly on these kinds of studies, all results must be reviewed with a skeptical eye and comparisons between different Phase II studies may not be accurate.

In the last decade, the availability of new, broadly active compounds, such as taxanes, vinorelbine, gemcitabine, and irinotecan, has represented an important gain in the management of CUP. In a Phase II trial, Briasoulis et al[21] evaluated the combination of carboplatin plus paclitaxel in 77 patients with CUP (including 33 patients with liver metastases, bone metastases, or multiorgan metastases). The ORR was 38.7% (CR rate, 20%) and the median OS was 13 months in the entire population and 10 months in the poor-prognosis group (visceral or disseminated metas-

tases). It is noteworthy that the 68.4% of patients who presented with peritoneal carcinomatosis may have contributed to the better results. A large group of patients with CUP (396 patients), excluding favorable subsets, was treated with taxane-containing regimens in 5 consecutive Phase II trials by the Minnie Pearl Cancer Research Network.[22–25] Overall, those 5 studies had an ORR of 30%, a median OS of 9.1 months, a progression-free survival of 5 months, 1-year and 2-year survival rates of 38% and 19%, respectively. The authors compared their results with historic data from 45 prospective trials (1515 patients) and with retrospective reviews (31,419 patients), which showed that the 1-year and 2-year survival rates were prolonged significantly.[26]

Within the group of new agents, gemcitabine can be considered a good candidate for polychemotherapy regimens in the treatment of CUP because of its wide spectrum of activity and good tolerability profile. Initially, this drug was given as second-line treatment.[27] More recently, on the basis of these encouraging results published in 2001 and confirmed in 2005,[28] gemcitabine has been investigated more largely investigated in the first-line setting.

Balana et al[29] conducted a Phase II study in 30 patients who had CUP with poor prognostic features

(10% of patients had brain metastases, 30% of patients had bone metastases and 20% of patients had liver metastases) to evaluate a regimen of cisplatin, etoposide and gemcitabine every 21 days. Those investigators reported an ORR of 36.6% and a median survival of 7.21 months with grade 3 or 4 neutropenia in 60% of patients.

In the study of Culine et al,[30] 80 patients (60% with poor prognostic features) were randomized to receive either cisplatin in combination with gemcitabine (GC) or irinotecan (IC). The reported ORR was 55% in the GC arm and 38% in the IC arm and the median survival was 8 months and 6 months, respectively, with an unfavorable toxicity profile in the IC group (2 toxic deaths from septic shock).

In 2004, Piga et al[31] confirmed response and survival data when using a platinum-containing regimen (carboplatin, doxorubicin, and etoposide) in a Phase II study of 102 patients with CUP. An ORR of 26.5% and an OS of 9 months (progression-free survival, 4 months) were reported, whereas the main toxicity was grade 3 or 4 hematologic toxicity, which was reported in 57.8% of patients.

Vinorelbine has shown good activity in patients with lung, breast, head/neck, ovarian and uterine carcinomas and has an acceptable toxicity profile. Few studies have evaluated the role of this drug in the treatment of CUP. Recently, in a randomized Phase II trial results that have been published only in an abstract form, Huebner et al[32] treated 92 patients with CUP using either paclitaxel plus carboplatin or gemcitabine plus vinorelbine. In those 2 treatment arms, the ORR was 21.6% and 21.4%, respectively; the median OS was 10.7 months and 6.9 months, respectively; and the median progression-free survival was 6.4 months and 4 months, respectively.

Because of this background and considering that most CUPs have their origin either in the pancreas or in the lung,[33] there was a strong rationale for designing a study in which cisplatin and gemcitabine were combined with either paclitaxel or vinorelbine. Overall, in the current study, the patients were a good prognostic group for CUP because of the following characteristics: relatively young age (60 years), good PS (0 or 1 for nearly all patients), prevalence of histology with a better prognosis (adenocarcinoma, 72.7%; squamous cell carcinoma, 10.6%), relatively few patients with liver involvement (27.3%) and many patients with only 1 metastatic site (56%).

In this cohort both combinations, CGT and CGV, satisfied the 2-step design and demonstrated antitumor activity without any relevant differences observed between them in terms of ORR (48.5% vs 42.3%) or response duration (7.5 months vs 7.4 months). How-ever, the CGV arm yielded superior results in terms of both OS (13.6 months vs 9.6 months) and treatment tolerability. Grade 3 and 4 neutropenia was only observed in 18.2% of patients on the CGT arm and in 12% of patients on the CGV arm. No febrile neutropenia was observed. Nausea and emesis, which generally were mild, were more frequent in the CGT group than in the CGV group. No toxic deaths were observed.

Our findings confirm that cisplatin, gemcitabine, paclitaxel and vinorelbine are active in patients with CUP. Even though survival is not an endpoint for a Phase II study, the survival results observed for the vinorelbine-containing combination appear to be extremely noteworthy, because they match the best results reported in the literature to date. Furthermore, the good tolerability profile of the vinorelbine-containing combination is a fundamental element to take into account when treating patients with a poor life expectancy, like that for patients with CUP. It must be taken into consideration that, as mentioned above, patient selection can interfere significantly with the results of a randomized Phase II study, depending on the prognostic characteristics of the patients who are selected. In conclusion, through lack of a deeper knowledge of the biologic and molecular characteristics of these particular neoplasms and according to a *pick the winner* attitude, we believe that the combination of CGV deserves consideration as an experimental arm in the design of future randomized, Phase III trials for patients with CUP.

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