Carboplatin Plus Paclitaxel in Unknown Primary Carcinoma: A Phase II Hellenic Cooperative Oncology Group Study

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Purpose: **To evaluate the efficacy of the carboplatin/paclitaxel combination in patients with carcinoma of unknown primary site (CUP).**

Patients and Methods: **Seventy-seven consecutive CUP patients (45 women and 32 men; median age, 60 years) were treated with carboplatin at target area under the curve 6 mg/mL/min followed by paclitaxel 200 mg/m^2 as a 3-hour infusion and granulocyte colony-stimulating factor from days 5 to 12. Treatment courses were repeated every 3 weeks to a maximum of eight cycles. Forty-seven patients had adenocarcinomas, 27 had undifferentiated carcinomas, and three had squamous cell carcinomas. Thirty-three patients presented with liver, bone, or multiple organ metastases, 23 with predominantly nodal/pleural disease, and 19 (16 women) with peritoneal carcinomatosis.**

Results: **The overall response rate by intent-to-treat analysis was 38.7% (95% confidence interval, 27.5% to 49.9%). There were no differences in response between adenocarcinomas and undifferentiated carcinomas, but efficacy varied among clinical subsets. The response rates and median survival times in the three clinically defined subsets were 47.8% and 13 months, respectively, for patients with predominantly nodal/pleural disease, 68.4% and 15 months, respectively, in women with peritoneal carcinomatosis, and 15.1% and 10 months, respectively, in patients with visceral or disseminated metastases. Chemotherapy was well-tolerated.**

Conclusion: **Carboplatin plus paclitaxel combination chemotherapy is effective in patients with predominantly nodal/pleural metastases of unknown primary carcinoma and in women with peritoneal carcinomatosis. However, in patients with liver, bone, or multiple organ involvement, the combination offers limited benefit. The investigation of novel treatment approaches is highly warranted for this group of patients.**

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CANCER OF UNKNOWN primary site (CUP) consists of a heterogeneous group of tumors that have acquired the capacity to metastasize before the development of a clinically evident primary lesion. These tumors are not rare; they represent almost 3% of all malignancies diagnosed in everyday oncology practice.[1]

Notable advances have been made over the past years in the treatment of well-defined clinical subgroups of CUP, such as women with peritoneal carcinomatosis and young adults with poorly differentiated carcinomas of midline distribution, but for the majority of patients prognosis still remains poor.[2]

In this study, we took into clinical testing the carboplatin/paclitaxel combination. The rationale for choosing this combination was based on available clinical and in vitro data. Mitotic spindle poison paclitaxel has shown considerable clinical activity in various malignant tumors including lung, breast, ovarian, and head/neck cancer, and it has been evaluated in vitro among the most active single agents in adenocarcinoma of unknown primary cell lines.[3] Besides, paclitaxel has shown to retain its activity in tumors with mutated *p53* and overexpressed *bcl-2* genes,[4-6] which is considered a molecular characteristic of CUP tumors.[7] Carboplatin has proven as equally effective as cisplatin in the chemosensitive CUP subsets with the additional advantage of being better tolerated and more convenient in clinical practice. We also had previously studied a triple combination of carboplatin, etoposide, and epirubicin that gave results that compare favorably with other cisplatin-based regimens.[8]

PATIENTS AND METHODS

This was the second multicenter nonrandomized phase II trial of the Hellenic Cooperative Oncology Group (HeCOG) on unknown primary tumors. This study opened in February 1996 and closed in February 1999, and a total of 77 patients with metastatic carcinoma of unknown origin were enrolled at seven participating HeCOG centers (Table 1). Forty-five patients were men and 32 were women, with a median age of 60 years and a performance status of 1. All patients underwent evaluation by one of the investigators and were registered with the HeCOG data management central office before treatment initiation.

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Table 1. Study Characteristics

Characteristic		No. of Patients
No. accrued		77
No. assessable		75
Sex		
Female		45
Male		32
Age, years		
Median	60	
Range	30-78	
PS		
Median	1	
Range	0-2	
Histology		
Adenocarcinoma		47
Well- and moderately differentiated		33
Poorly differentiated		14
Undifferentiated carcinoma		27
Squamous cell carcinoma		3
Metastatic sites at presentation		
Lymph nodes		34
Only nodal disease		13
Nodes + limited lung or pleura		7
Liver		19
Only liver metastases		4
Abdomen		26
Only peritoneal		17
Lung		11
Pleura		12
Only pleural		3
Bones		9
Skin		2
Brain		3
Adrenal		6
Multiple (≥ 3) sites		17
No. of courses given		
Median	6	
Range	1-8	

Eligibility Criteria

Patients with metastatic carcinoma of unknown origin were eligible for study entry if they fulfilled the following criteria of the CUP definition: histologically or cytologically diagnosed metastatic carcinoma for which a complete history, detailed clinical examination, blood chemistry, urinalysis, test for occult blood in stools, chest radiograph, abdomen and pelvis computed tomography, and symptom- or sign-directed imaging or endoscopic studies failed to reveal the site of origin of the metastatic disease. Directed studies included bronchoscopy in case of positive chest radiograph or pulmonary symptoms, nose and pharyngeal endoscopy in case of localization of metastases in cervical lymph nodes, gastrointestinal endoscopy in case of abdominal complaints, and laparoscopy plus tumor debulking in case of abdominal carcinomatosis.

An extensive immunohistochemical study was required in all cases of undifferentiated carcinoma or poorly differentiated adenocarcinoma with the use of a wide range of immunoperoxidase markers. This aimed to minimize the possibility of a misdiagnosis of other malignancies such as non-Hodgkin's lymphomas, extragonadal germ cell tumors, malignant melanomas, and undifferentiated sarcomas. The most commonly used markers were the leukocyte common antigen, cytokeratins 7 and 20, neuroendocrine markers as neuron-specific enolase or chromogranin, *S*-100 protein, and vimentin. Staining for prostate-specific antigen in men and for estrogen- and progesterone-receptor proteins in women was required to be performed in most cases regardless of the histopathologic type (adenocarcinoma or undifferentiated carcinoma).

Hematologic and biochemical screening was performed in all patients, and six serum tumor markers (alpha-fetoprotein [AFP], human chorionic gonadotropin beta-subunit [β-HCG], CA-125, CA 15–3, CA 19–9, and carcinoembryonic antigen [CEA]) were assessed in most of the cases. AFP, β-HCG, and prostate-specific antigen serum markers were required at baseline evaluation of male patients, in the context of clinical and pathologic data.

Patients were required to have measurable or assessable disease assessed by radiologic evaluation within 14 days of enrollment. It was also required to have a minimum life expectancy of 3 months and a World Health Organization performance status of 0 to 2. Patients had to be chemotherapy-naïve, be aged 18 to 75 years, and have adequate hematologic, renal, and hepatic functions defined by a granulocyte count greater than 1.5×10^9/L, platelet count greater than 150×10^9/L, serum creatinine level within normal limits, bilirubin level less than 1.5 times the upper normal limit, and AST two times the upper normal limit in patients without liver metastases and five times the upper normal limit in patients with documented liver metastases. Patients were excluded if any of the following conditions were present: cardiac arrhythmias, symptomatic heart failure, history of myocardial infarction, pre-existing neuropathy, newly documented brain metastases, and serious illnesses including uncontrolled infections and psychiatric disorders. Female patients with adenocarcinoma involving only axillary lymph nodes were excluded from this study. All patients were required to give informed consent and be registered with the HeCOG central office before treatment initiation.

Subgroup Definition

Patients were categorized into the following three subgroups on the basis of sites of metastases at presentation: (1) patients with liver or bone or disseminated visceral metastases, (2) patients with predominantly nodal or pleural disease, and (3) patients with peritoneal carcinomatosis. In the predominantly nodal/pleural disease subgroup, there were patients included with only nodal or only pleural disease and patients with largely nodal metastases and a limited lung or pleural involvement.

Treatment

Carboplatin was administered by a 30-minute intravenous infusion, dosed at a 6 mg/mL/min target AUC (area under the free carboplatin plasma concentration versus time curve), and was followed by paclitaxel 200 mg/m^2 in 500 mL of normal saline administered over 3 hours. The Calvert formula was used for carboplatin dosing, based on glomerular filtration rate calculated by serum creatinine, body surface, and age.[9,10] The following antiallergic premedication scheme was administered in all patients before chemotherapy to avoid paclitaxel-related hypersensitivity reactions: 32 mg methylprednisolone was taken orally 24 and 12 hours before treatment and then 10 minutes before start of carboplatin infusion; and dexamethasone 16 mg, dimethindene maleate (1 mg/10 kg body weight) or diphenhydramine 50 mg, and ranitidine 100 mg were administered intravenously over 10 minutes. A single 8-mg intravenous dose of ondansetron was given in all patients as an antiemetic after the antiallergic schema. Prophylactic subcutaneous filgrastim (granulocyte colony-stimulating factor [G-CSF]) 300 μg was suggested to be administered on days

5 to 12 of each cycle. Concomitant radiotherapy for symptom control in the absence of disease progression was allowed, but the protocol drugs were held for at least 2 weeks after irradiation.

Chemotherapy cycles were repeated every 3 weeks in the lack of any toxicity greater than grade 1. Responding patients could receive a total of eight courses, and patients with stable disease had a six-cycle maximum.

Dose Modification Guidelines

According to the protocol, treatment delays and dose modifications were based on complete blood cell counts taken on the day of planned next treatment, as well as any febrile neutropenia or organ-specific toxicity occurring at any time during therapy. For retreatment, it was necessary for any toxicity to have settled down to a minimum grade 1. A treatment delay for a maximum of 14 days was allowed until ANC reached a minimum of $\geq 1{,}500/\mu L$ and platelets reached a minimum of $\geq 100{,}000/\mu L$. In case of grade 2 hematologic toxicity, the dose of paclitaxel at the following cycles was decreased to 90% and carboplatin was decreased to AUC 5; in case of grade 3 and 4 hematologic toxicity, drug doses were decreased to 75% for paclitaxel and AUC 4 for carboplatin. A similar dose reduction scale was also used for diarrhea. Any other grade 2 or higher organ-specific toxicity was considered a reason for treatment discontinuation.

Toxicity and Response Evaluation

For toxicity, the National Cancer Institute common toxicity criteria were adopted, and for efficacy assessment, World Health Organization criteria were used.[11] Patients were evaluated for efficacy every two cycles. For characterization of complete response, total disappearance of all measurable and assessable disease was required; for partial remission a $\geq 50\%$ reduction in the size of all lesions as measured by the product of the greatest length and width of measurable lesions was required. Confirmation of objective responses was required in all cases at a minimum time interval of 4 weeks. Duration of response was calculated from the time the objective response was documented until the date of disease progression. Stable disease was measured from the start of the treatment until the criteria for progression were met, taking as reference the smallest measurements recorded since the treatment started.

Statistical Issues

Survival was calculated by Kaplan-Meier method and comparison of survival curves was performed by the log-rank test. The unpaired *t* test, logistic regression, and receiver-operator curves were used to compare the values of serum markers between two subgroups defined by response to treatment, and the one-way analysis of variance was used to compare the mean/median values of serum markers between the three clinical subsets. The Graphpad Instat version 3 (GraphPad Software, Inc, San Diego, CA) and Prism version 2.01 software programs were used for statistical analysis and graphing.

RESULTS

Patient Characteristics

Patient characteristics are listed in Tables 1 and 2. Two patients were excluded from the final analysis as ineligible because a primary site was identified at a later time. These were two female patients with peritoneal (n = 1) and lymph nodal metastases (n = 1) who had both achieved a complete response. Pretreatment evaluation, including exploratory laparotomy in the case of a patient with peritoneal carcinomatosis, had failed to identify a primary site in either case. Two and 4 months after treatment completion, the two female patients underwent an exploratory laparotomy on the indications of abdominal and pelvic computed tomography scan; an ovarian primary tumor was found in one patient, and an endometrial primary tumor was found in the other patient.

Table 2. Characteristics of Clinical Subtypes

Clinical Subtype	No. of Patients			Age (years)		Histology (no. of patients)		
	Total	Women	Men	Mean	Range	A	U	S
Liver/bone or disseminated metastases	33	15	18	59	33-71	22	9	2
Predominantly nodal/pleural disease	23	12	11	54	43-73	9	13	1
Peritoneal carcinomatosis	19	16	3	64	30-72	14	5	0

Abbreviations: A, adenocarcinoma; U, undifferentiated carcinoma; S, squamous cell carcinoma.

Between the 75 eligible patients, 17 (22.6%) had three or more metastatic sites at presentation, 21 had two, and 37 patients had only one organ involvement as follows: peritoneal (n = 17), lymph nodes (n =13), liver (n = 4), and pleural-only metastases (n = 3). By histopathologic criteria, patients were assigned to the following three groups: adenocarcinomas (47 patients), undifferentiated carcinomas (27 patients), and squamous-cell carcinomas (three patients). By clinical criteria, they were categorized into three groups (defined as CUP subsets) as follows: 33 patients presented with liver, bone, or multiorgan metastases (visceral or widespread disease), 23 presented with a predominantly nodal/pleural disease, and 19 (16 women) presented with peritoneal carcinomatosis. In the subset of primary lymph nodal/pleural disease, there were included 13 patients with lymph node–only involvement, three patients with pleural-only disease, and seven patients who had bulky nodal disease combined with either limited lung infiltrations (n = 3) or pleural effusion (n = 4). The majority of patients with lymph node–only metastases had multiple nodal groups involved at presentation; one patient had only limited supraclavicular adenopathy, two patients presented with inguinal, and two presented with head-neck lymph node metastases. The number of women clearly surpassed the number of men in the subset of peritoneal carcinomatosis. Otherwise, demographic data did not differ significantly between the three clinical subsets.

Treatment Delivery

A total of 393 cycles of therapy were given on this trial, and patients received a median six cycles of treatment (range, one to eight cycles). The most common reason for stopping

Table 3. Efficacy of Carboplatin Plus Paclitaxel in Patients With CUP

	ITT		Assessable Patients		No. of Objective Responses			Response Duration (months)	
	No. of Patients	RR (%)	No. of Patients	RR (%)	Total	CR	PR	Median	Range
Overall	75	38.7	70	41.4	29	15	14	6	3-45+
Efficacy by histology									
Adenocarcinoma	45	40.0	42	42.8	18	11	7	7	2-30+
Undifferentiated carcinoma	27	37.0	26	38.5	10	4	6	6	4-45
Squamous cell carcinoma	3	30.0	3	30.0	1	1	0	3	
Efficacy by CUP subtype									
Liver or disseminated metastases	33	15.1	31	16.1	5	0	5	5	3-6
Nodal/pleural disease	23	47.8	23	47.8	11	6	5	8	4-45
Peritoneal carcinomatosis	19	68.4	16	81.2	13	9	4	7	3-30+

Abbreviations: ITT, by intent-to-treat evaluation; RR, response rate; CR, compete response; PR, partial response.

treatment was disease progression, but toxicity also led to early termination in three additional patients. Eight treatment-responding patients received eight courses of chemotherapy.

The median received dose was the planned dose. Dose modification was made necessary because of toxicity in a few cases; five patients were treated at 4-week intervals, and three and two patients had a 10% and 25% dose deduction, respectively.

Efficacy

Seventy patients who received the carboplatin/paclitaxel combination according to protocol were assessable for response. Five patients were excluded for the following reasons: two opted to withdraw from the study therapy voluntarily after the first cycle, and three were dropped off the study because of toxicity-related treatment discontinuation.

By intent-to-treat analysis, the overall response rate was 38.7% (95% confidence interval, 27.5% to 49.9%) and was marginally better in efficacy-assessable patients (41.4%). There was no difference in antitumor activity between the two major histopathologic types, the adenocarcinomas and undifferentiated carcinomas. On the contrary, the observed objective response rate differed significantly among the three clinical subsets; 47.8% of patients with predominantly nodal disease, 68.4% of peritoneal carcinomatosis patients, and only 15.1% of patients with widespread multiorgan involvement responded to treatment (Table 3). Regarding peritoneal carcinomatosis, one out of three male patients achieved an objective response that lasted a median 7 months, whereas a 75% objective response rate was documented in women of this clinical subset.

Thirty-three patients were offered a second-line therapy for having a primary resistant tumor or on relapse. Specifically, in the subset of multimetastatic disease, 16 patients were rechallenged with second-line chemotherapy. Seven patients were treated with a mitomycin/fluorouracil combination, five patients received gemcitabine, and four patients received other agents. No objective responses were observed; however, four cases of disease stabilization were seen.

A relatively high figure of complete responses (20%) was seen in this study, with a median response duration of 5 to 8 months. Five patients enjoyed a progression-free survival longer than 2 years, two patients with peritoneal carcinomatosis (30 and 30+ months) and three patients with nodal disease (45, 25, and 23+ months) (Fig 1). At a median follow-up time of 28 months, the overall median survival was 13 months. In the two favorable subsets, the nodal disease and peritoneal carcinomatosis, median survival was 13 and 15 months, respectively; whereas, in the poor prognosis group of visceral or disseminated metastases, it was only 10 months (Fig 2). A difference of statistical significance was observed between the survival of patients in the visceral/disseminated group and those in the lymph nodal group in favor of the latter group (10 *v* 15 months, respectively; $P = .001$).

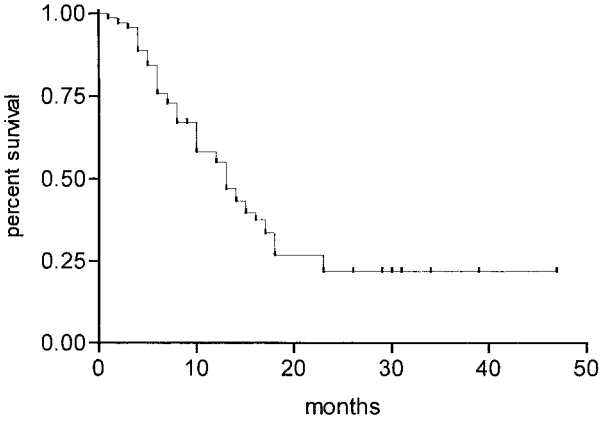

Fig 1. Survival curve of the 75 enrolled patients (median survival, 13 months).

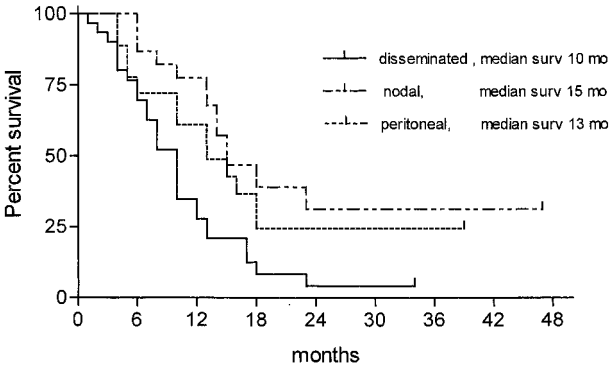

Fig 2. Actuarial survival curves for the 3 subsets. The log-rank test between the visceral/bone group and the nodal group showed a significant difference ($P = .001$).

Toxicity

Toxicity data are listed in Table 4. Three major toxicity events were recorded in this study. Two patients, who were not given prophylactic G-CSF, died of septic granulocytopenia after the first and third courses of treatment. A 72-year-old patient with peritoneal carcinomatosis died of cardiopulmonary failure after the fifth course. This toxicity cannot be clearly attributed to the study treatment because of a disputable cardiologic history of this patient. Otherwise, toxicity was not a major issue in this study, and the majority of patients tolerated treatment well. With the exception of alopecia, the most common recorded toxicity was mild to moderate neurotoxicity. Because the majority of patients received prophylactic G-CSF, myelotoxicity was rare, and dose modification was made necessary in only six cases.

Serum Markers

Six serum tumor markers were assessed in baseline pretreatment evaluation in 60 patients in this study. CA-125 was assessed in 47 patients, CA 15–3 in 35, CEA in 49, CA 19–9 in 50, β-HCG in 14, and AFP in 34 patients. In 57% of the cases, multiple markers were found elevated at diagnosis (more than two out of three or three out of four assessed). We did not manage to detect any specific pattern of combination of serum marker elevations that could be ascribed to any particular clinical or histologic CUP subgroup. In addition, we did detect a meaningful difference between the three clinical subsets. Nevertheless, CA-125 values were only marginally higher in the group of patients who responded to therapy (medial values, 179 *v* 307 U/mL), and CEA, CA 15–3, and CA 19–9 were marginal higher in nonresponding patients. These differences were not statistically significant.

Table 4. Carboplatin/Paclitaxel Combination in CUP: Toxicity Reported as Worst Grade per Patient (N = 73)

	Patients With Toxicity Grade						
	I		II		III		IV
Toxicity*	No.	%	No.	%	No.	%	(no.)
Anemia			1		2		
Thrombopenia			1		1		1
Granulocytopenia			5	6.8	3	4.1	2†
Neurotoxicity	19	26.4	12	16.4	3	4.1	
Myalgia	6	8.2	3	4.1			
Diarrhea	2		1		1		
Cardiologic					1		1‡
Alopecia§	30	41	39	54			

*National Cancer Institute common toxicity criteria.

†Both were septic deaths.

‡Death by heart failure.

§A number of patients had received alopecia prophylaxis by scalp cooling system.

DISCUSSION

A diagnosis of metastatic carcinoma of unknown origin has long been considered synonymous with dismal prognosis.[12] With the exception of certain clinical subsets that have been identified during the last two decades for being substantially sensitive to platinum-containing treatment, no chemotherapy regimen has been established as standard first-line therapy for patients diagnosed with splanchnic or multiple-organ metastases of unknown primary site.[13,14] All chemotherapy regimens studied to date were designed empirically and ended up with disappointing results.[1,15]

In this study, we demonstrated an overall response rate of 38.7% (95% confidence interval, 27.5% to 49.9%) by an intent-to-treat analysis and a 41.4% response rate in CUP patients assessable for efficacy, who were treated with the carboplatin/paclitaxel combination given once every 3 weeks. This satisfactory antitumor activity is largely attributed to the high response rates recorded in the two favorable subsets that were included in this study (47.8% of patients with predominantly nodal disease and 75% of female patients with peritoneal carcinomatosis responded). Lymph nodal metastases, the number of metastatic sites, and histology have shown to influence survival in CUP patients[2]; whereas a favorable outcome to cisplatin treatment has been described for CUP patients who present with tumor location at mediastinum, retroperitoneum, and peripheral lymph nodes as compared with CUP location in other sites.[16]

Interestingly, in a retrospective study, cytogenetic or molecular fingerprints that refer to an extragonadal germ cell origin were identified in tumors of long-term responding patients with midline distribution.[17] In the present study, three patients (13%) with predominantly nodal disease had durable responses (45, 25, and 23+ months). The present data suggest that the carboplatin plus paclitaxel regimen demonstrates an equal efficacy with previously reported cisplatin- or carboplatin-based combinations in CUP patients with predominantly nodal metastases.[8,16]

Women with peritoneal carcinomatosis of unknown primary site at laparotomy constituted the other favorable CUP subset in this study. This subset of CUP has been identified as a distinct clinical entity that has a more indolent disease course and expresses a higher response rate to systemic therapy with chances for long-term, disease-free survival.[18] Indeed, in this group of patients, we obtained an encouraging 75% response rate, with nine complete responses and a median duration of response of 7 months. These results are comparable with those obtained with the same combination in ovarian carcinoma patients.[19,20] Nevertheless, the obtained median survival of 13 months cannot be considered satisfactory for this favorable subset of CUP patients.

Hainsworth et al,[21] from the Minnie Pearl Cancer Treatment Network, have reported, using a triple combination chemotherapy regimen with paclitaxel, carboplatin, and protracted oral etoposide, an encouraging 47% response rate and a median survival of 13.4 months in 53 assessable CUP patients. In a recently updated report on this study, the median survival dropped to 11 months; but again, interestingly, 18% of patients remained in a progression-free status for more than 2 years.[22] Those investigators did not detect a difference in activity between the histologic subtypes, as was the case in our study as well. In general, our results are consistent with the results of the Minnie Pearl Cancer Treatment Network study, particularly in regard to efficacy. Regarding patients with liver, bone, or multiorgan involvement, a poor response rate (15.1%) was recorded. Although such a finding was not clearly defined in that study, activity was poor in the small number of cases of patients with liver or bone metastases (22% and 0%, respectively). A 10-month median survival was achieved in this poor-prognosis group of patients treated with the carboplatin/paclitaxel combination in our study. This is considered a rather satisfactory survival figure compared with historical data and indicates a possible treatment-derived benefit, notwithstanding the low objective response rate.

The comparable efficacy in these two trials questions the role of the addition of etoposide in the combination of carboplatin plus paclitaxel in the treatment of CUP. It had previously been suggested in a retrospective study that etoposide makes a significant impact in the therapy of poorly differentiated CUP.[23] Nevertheless, other investigators have reported a poor activity of the combination of cisplatin with continuous-infusion etoposide,[24] and in a recently published study, the combination of carboplatin plus prolonged oral etoposide on days 1 to 20 demonstrated only poor antitumor activity in patients with CUP (response rate, 23%; median survival, 5.6 months).[25]

In published literature, there is only limited, if any, evidence in support of superiority of any combination or single agent in nonfavorable CUP subsets. In most of the studies, the median survival has ranged from 5.4 to 11 months, and the response rate is lower than 25%.[15,25-27] Furthermore, high-dose chemotherapy, with a combination of cyclophosphamide, etoposide, carboplatin, and doxorubicin, failed to demonstrate an improved outcome in patients with disseminated CUP.[28]

In conclusion, we suggest that the carboplatin plus paclitaxel combination represents an effective therapy for patients with predominantly nodal/pleural metastases of unknown primary carcinoma and for women with peritoneal carcinomatosis of unidentifiable origin at laparotomy. For CUP patients who present with liver, bone, or multiple organ involvement, this treatment offers only limited benefit. More clinical studies are under way that incorporate novel chemotherapy agents that are expected to expand our treatment armamentarium for CUP. However, only when we will be able to move on from empiric chemotherapy to more innovative and rationally built treatment approaches, based on translational studies, we may expect a true optimistic outlook for this group of patients.

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