Phase II Trial of Carboplatin, Gemcitabine, and Capecitabine in Patients With Carcinoma of Unknown Primary Site

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BACKGROUND. The purposes of this study were to evaluate efficacy and toxicity of the combination of carboplatin, gemcitabine, and capecitabine in patients with carcinoma of unknown primary site (CUP).

METHODS. Patients with CUP received carboplatin AUC 5 mg/mL a minute intravenously Day 1, gemcitabine 1000 mg/m^2 intravenously Days 1 and 8, and capecitabine 1600 mg/m^2 orally in divided doses, Days 1–14 of a 21-day cycle for up to 8 cycles. The primary endpoint of the study was objective response rate by intent-to-treat analysis.

RESULTS. Thirty-three patients were treated (median age, 58 years; men:women ratio, 19:14). Most patients had a baseline performance status of 1. The objective response rate was 39.4% (95% CI, 22.9%–57.9%) in all patients, 36.4% in 22 patients with well to moderately differentiated adenocarcinoma, and 40.0% in 20 patients with liver metastases. Median progression-free survival time was 6.2 months (95% CI, 5.4%–8.0%), and median survival time was 7.6 months (95% CI, 6.3–14.1). One and 2-year survival rates were 35.6% and 14.2%, respectively. The most frequent grade $\geq$3 adverse events were neutropenia (67%), thrombocytopenia (48%), and anemia (33%).

CONCLUSIONS. The combination of carboplatin, gemcitabine, and capecitabine is active in CUP, especially in patients with liver metastases. This regimen may be a potential therapy for CUP patients with good performance status, particularly those with a suspected origin below the diaphragm. ***Cancer*** **2007;110:770–5.**

KEYWORDS: carcinoma of unknown primary, chemotherapy, experimental therapeutics, gemcitabine, capecitabine.

Carcinoma of unknown primary site (CUP) accounted for approximately 2% of all malignancies diagnosed in the United States in 2006.[1] Patients with CUP are a heterogeneous group, with histologic subtypes including adenocarcinoma with various degrees of differentiation, squamous cell carcinoma, poorly differentiated carcinoma, and neuroendocrine cancer. Patients with CUP present with metastatic disease, most commonly involving liver, lung, and/or bone. The primary site is ultimately identified in only 15%–35% of patients.[2,3] Autopsy series have suggested the lung, pancreas, and hepatobiliary tree as the most common sites of disease origin.[4]

There is no single regimen or approach to date that has demonstrated significant prolongation of survival in patients with CUP. Progress has been made in identifying subgroups within this designation (eg, undifferentiated or neuroendocrine carcinomas) that may benefit from specific therapy.[5,6] However, for the relatively

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common clinical scenario of a patient presenting with well or moderately differentiated adenocarcinoma involving the liver, prognosis remains poor despite therapy.[7–9]

Cisplatin and its analog, carboplatin, are often used in chemotherapy combinations to treat CUP. Gemcitabine has demonstrated activity in pancreaticobiliary, breast, and nonsmall cell lung carcinomas, as well as in carcinomas of unknown primary site.[10,11] There is evidence of in vitro and in vivo synergy between gemcitabine and the platinum compounds.[12,13] In addition, gemcitabine enhances the activity of 5-fluorouracil in vivo.[14] Capecitabine is an orally administered fluoropyrimidine that mimics the efficacy, tolerance, and toxicity observed with low-dose, continuous-infusion 5-fluorouracil. Concomitant administration of gemcitabine and capecitabine may result in increased cytotoxicity by reducing intracellular deoxythymidine triphosphate concentrations through different mechanisms, thereby inhibiting DNA replication and repair and potentiating the activity of carboplatin. Furthermore, this 3-drug combination provides a convenient schedule of brief intravenous treatment that is suitable for palliative treatment programs in the outpatient setting. With these considerations, we designed this study to evaluate the efficacy and toxicity of carboplatin, gemcitabine, and capecitabine in patients with CUP. The primary objective of this study was to estimate objective tumor-response rate with secondary objectives including characterization of toxicity and assessment of survival.

MATERIALS AND METHODS

Eligibility

Eligibility criteria included cytologic or histologic confirmation of metastatic carcinoma with the primary site not identified after a complete history and physical examination, laboratory evaluation (serum β-HCG [human chorionic gonadotropin], serum α-fetoprotein, and serum prostate-specific antigen in men), and radiologic studies (computed tomography of the chest, abdomen and pelvis, mammography in women). In addition, immunohistochemical staining of the tumor tissue, including studies for estrogen and/or progesterone receptors and prostate-specific antigen, were performed as clinically appropriate. Further eligibility criteria included ages 18 years or older, Zubrod performance status (PS) $\leq$2, and adequate organ function as defined by neutrophils $\geq$1500/mm^3, platelets $\geq$100,000/mm^3, serum creatinine $\leq$2.0 mg/dL, and bilirubin $\leq$1.5 mg/dL. Patients with reproductive potential were required to use effective contraception during treatment. One prior chemotherapy regimen was allowed, provided it did not contain carboplatin, gemcitabine, or capecitabine.

Patients with known brain metastases were ineligible. Patients with a subset of CUP appropriate for a well-defined treatment approach (isolated squamous cell carcinoma of the cervical lymph nodes, women with isolated axillary lymphadenopathy or predominant peritoneal carcinomatosis, men < 50 years of age with poorly differentiated carcinoma in the mediastinum and/or retroperitoneum) were excluded. In addition, patients could not have another active systemic malignancy or any serious comorbid medical or psychiatric condition that could interfere with the safe delivery of therapy. The institutional review boards of the University of Michigan Medical School (Ann Arbor, Mich) and Wayne State University (Detroit, Mich) approved the trial. Written informed consent was obtained from all patients before initiation of therapy.

Treatment

Treatment comprised 21-day cycles of carboplatin (Bristol-Myers Squibb, Princeton, NJ), gemcitabine (Eli Lilly, Indianapolis, Ind), and capecitabine (Roche, Nutley, NJ). Carboplatin dose was targeted to an area under the curve (AUC) of 5 mg/mL x minute (as per the Calvert formula) and was given as a 30-minute intravenous infusion after gemcitabine on Day 1. Gemcitabine 1000 mg/m^2 was administered as a 30-minute intravenous infusion on Days 1 and 8. Capecitabine was taken orally twice daily for 14 days beginning on Day 1 at a daily divided dose of 1600 mg/m^2 rounded to the nearest 500 mg. Morning and evening doses were taken 11 to 13 hours apart with the odd tablet added to the morning dose, if necessary. Hematopoietic growth-factor support was not given with the first treatment cycle but was permitted with subsequent cycles.

Dose Adjustments for Toxicity

Toxicity was evaluated according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC version 2.0). A cycle of treatment could begin when absolute neutrophil count (ANC) was $\geq$1500/mm^3, platelets were $\geq$100,000/mm^3, and nonhematologic toxicity had resolved to $\leq$grade 1. Only gemcitabine and carboplatin doses were adjusted for hematologic toxicity. On Day 8, gemcitabine was given at full dose for ANC $\geq$1000/mm^3 and platelets $\geq$75,000/mm^3. For ANC $\geq$500/mm^3 and <1000/mm^3 or platelets >51,000/mm^3 and <75,000/mm^3, gemcitabine dose was reduced 50%. Gemcitabine was dropped on Day 8 for ANC <500/mm^3 or platelets

$\leq$50,000/mm^3. If a gemcitabine dose was dropped on Day 8, carboplatin and gemcitabine doses were reduced by 20% in subsequent cycles. Blood counts were measured on Day 15 during cycles 1 and 2, and if a patient experienced grade 4 thrombocytopenia at any point in the cycle, subsequent doses of carboplatin and gemcitabine were reduced by 20%.

Patients who experienced capecitabine-related toxicity $\geq$grade 2 (diarrhea, stomatitis, esophagitis, or hand-and-foot syndrome) had capecitabine held until recovery to $\leq$grade 1, and subsequent cycles were dose-reduced by 25% for grade 2 and by 50% for grade 3 or 4 toxicities. If agent nonspecific $\geq$grade 3 nonhematologic toxicity was observed at any point, treatment was held until recovery to $\leq$grade 1, and all drugs were dose-reduced by 20% for subsequent cycles. Dose re-escalation was not permitted with the exception of Day 8 gemcitabine-dose reductions.

Treatment continued for up to 8 cycles with demonstration of objective response or disease stability. Patients were evaluated for response according to Response Evaluation Criteria In Solid Tumors (RECIST) guidelines every 2 cycles.[15] Criteria for removal from study included clinical or radiological evidence of progressive disease, patient refusal to continue therapy, treatment interruption $>$ 2 weeks, or unacceptable toxicity.

Statistical Methods

This clinical trial used a standard Minimax 2-stage design, whereby the response rate to treatment was the primary endpoint.[16] Response was defined as a complete or partial overall best response within 6 months from the beginning of therapy. For design purposes, a response rate of 40% was considered clinically meaningful; a rate of 20% was considered clinically insignificant. The total sample size was 33 patients to allow 80% statistical power to detect such a difference in response.

All patients enrolled on the trial were considered for calculation of the response to treatment following the intent-to-treat paradigm. Response rate was reported as a percentage, along with exact binomial confidence intervals. Survival, progression-free survival, and time-to-treatment-failure were summarized by the Kaplan and Meier product-limit method. For each time-dependent endpoint, the time interval was calculated from the date of treatment initiation until the date of death, death or disease progression, or treatment failure, respectively. Patients who did not reach the endpoint of interest were censored at the date of their last clinical follow-up. Tumor-control rate was defined as stable disease or response at 3 months from treatment initiation. All statistical analyses were conducted with SAS software (version 9.12; SAS Institute, Chicago, Ill), and *P*-values $\leq$.05 were considered statistically significant.

RESULTS

Thirty-three patients were enrolled onto the study between August 2001 and January 2006. Data were collected until September 1, 2006. Patient characteristics are summarized in Table 1. The median age at study entry was 58 years (range, 21–73 years). No patient had received prior chemotherapy or radiation for CUP. Ten patients had 3 or more metastatic sites, 11 had 2 metastatic sites, and 12 patients had only 1 site of disease that included liver (n = 5), lymph nodes (n = 3), and peritoneal cavity (n = 4). The majority (76%) of patients presented with visceral disease. Seventy-three percent of the patients demonstrated a performance score (PS) of 0 or 1. Upon histological review, patients were categorized into 1 of 4 groups, well to moderately differentiated adenocarcinoma (n = 22), poorly differentiated adenocarcinoma (n = 5), undifferentiated carcinoma (n = 5), and squamous cell carcinoma (n = 1).

Toxicity

A median of 5 cycles was administered to each patient (range, 1–8). Five (15%) patients completed $<$ 2 cycles of therapy. There were 2 early deaths; 1 patient died on Day 24, probably from a pulmonary embolus, and another patient died on Day 23 from neutropenic sepsis. Two patients discontinued treatment because of clinical evidence of early disease progression after the first cycle, and 1 patient requested removal from the study, primarily because of toxicity.

In general, the treatment was well tolerated. Toxicity data are listed in Table 2. The most common grade 3–4 toxicities were neutropenia (67%) and thrombocytopenia (48%). Seven (21%) patients had grade 4 thrombocytopenia, but none experienced bleeding, and only 1 was transfused with platelets. All 9 patients with a baseline PS of 2 experienced complicated hematologic or nonhematologic toxicity $\geq$ grade 3 compared with 10 of 24 (42%) patients with PS of 0–1. Twenty-three (70%) patients required at least 1 dose reduction of carboplatin and/or gemcitabine, 12 because of toxicity that occurred during cycle 1. Fourteen (42%) patients had a delay of treatment by 1 week, and 7 (21%) patients had the Day 8 dose of gemcitabine dropped once during treatment. Capecitabine was dose-reduced for stomatitis or diarrhea in 6 (18%) patients. Eighteen (54%) patients required hospitalization during study treatment, 10 (30%) for treatment-related toxicity (neutropenic

TABLE 1
Patient Characteristics

Characteristic	No.	%
Sex		
Men	19	58
Women	14	42
Age, y		
Median	58	
Range	21–73	
Race		
Caucasian	29	88
African American	2	6
Asian	1	3
Other	1	3
Performance status		
0	9	27
1	15	45
2	9	27
Histology		
Well to moderately differentiated adenocarcinoma	22	67
Poorly differentiated adenocarcinoma	5	15
Undifferentiated carcinoma	5	15
Squamous cell carcinoma	1	3
Metastatic sites at presentation		
Liver	20	61
Liver only	5	15
Lung	13	39
Abdomen	14	42
Peritoneal only	4	12
Lymph nodes	15	45
Lymph nodes only	3	9
Metastatic sites ≥3	10	30

TABLE 2
Worst Toxicity Experienced per Patient (n = 33) Grade

Toxicity	Grade 3	Grade 4	Grade 5
Anemia	11	0	0
Thrombocytopenia	9	7	0
Leukopenia	18	3	0
Neutropenia	10	12	0
Neutropenic fever	2	0	0
Nausea/Vomiting	5	1	0
Constipation	1	0	0
Diarrhea	1	0	0
Non-neutropenic fever	2	0	0
Sepsis	3	0	1
DVT/PE	2	0	1
Hepatotoxicity	1	0	0
Hand/Foot/Stomatitis	2	0	0
Fatigue/Decline in PS	2	0	0

DVT/PE indicates deep venous thrombosis/pulmonary embolism; PS, performance status.

fever/sepsis,[4] vomiting,[3] platelet transfusion, dehydration, diarrhea), 3 for small-bowel obstruction in the setting of disease progression, and 5 for other nontreatment-related reasons (pulmonary embolism,[3] non-neutropenic fever[2]).

Response and Survival

Thirteen of the 33 (39.4%; 95% CI, 22.9%–57.9%) registered patients had a partial response to treatment. Median response duration was 3.9 months (range, 1.4–11.2 months). In the 22 patients with well to moderately differentiated adenocarcinoma, the response rate was 36.4% (95% CI, 17.2%–59.3%), and in the 20 patients with liver metastasis, the response rate was 40% (95% CI, 19.1%–64.0%). In the 10 patients with poorly differentiated or undifferentiated carcinoma, the response rate was 50% (95% CI, 18.7%–81.3%). Twenty patients had a partial response or stable disease through 4 cycles of therapy for a tumor control rate of 60.6% (95% CI, 42.1%–77.1%). One patient with stable disease, according to RECIST guidelines, underwent surgical resection of the residual hepatic disease, which demonstrated a pathologically complete remission.

By using intent-to-treat analysis, the median time to treatment failure was 4.5 months (95% CI, 2.8–5.7). Median progression-free survival time was 6.2 months (95% CI, 5.4%–8.0%), and at 6 months, over half (54.5%; 95% CI, 36.3%–69.6%) of the patients were alive and progression free. Median survival was 7.6 months (95% CI, 6.3–14.1 months), and the 1-year and 2-year survival rates were 35.6% (95% CI, 19.7%–51.8%) and 14.2% (95% CI, 4.6%–29.1%), respectively. Four patients remained alive at 8.0 months, 9.4 months, 28.4 months, and 54.1 months from treatment initiation. The Kaplan-Meier estimates for overall and progression-free survival for the 33 enrolled patients are presented in Figure 1.

Serum Markers

Carcinoembryonic antigen (CEA) was assessed before treatment in 26 patients and at repeated post-therapy in 16 patients. Fourteen patients demonstrated an elevated CEA at presentation (range, 5.6–1150.0 ng/mL), and 6 (43%) had a 50% or greater reduction in CEA during therapy. The CA 19-9 tumor marker was evaluated before treatment in 23 patients and repeated in 13 patients. Fifteen patients demonstrated an elevated baseline CA 19-9 (range, 81–9829 U/mL), and 6 (40%) had a 50% or greater reduction in CA 19-9 during therapy. Patients with a ≥50% in an elevated serum marker survived longer than those with elevated markers without response (median survival, 19.4 months vs 7.1 months; $P = .03$).

DISCUSSION

In 1996, approximately 50,000 cases of CUP were diagnosed in the United States accounting for 5% of all cancers.[17] Currently, that number has been

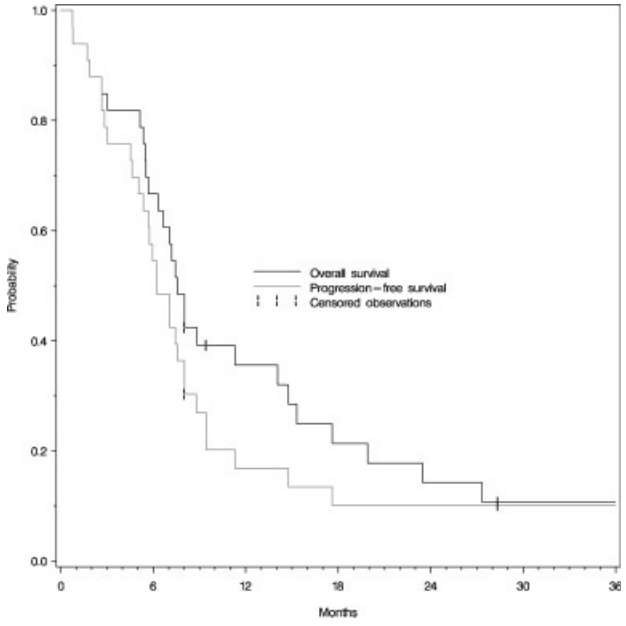

FIGURE 1. Kaplan-Meier product-limit estimates for overall and progression-free survival for all patients N = 33 (median overall survival, 7.6 months; median progression-free survival, 6.2 months).

reduced by more than half, mainly because of improvements and access to radiologic examinations and, more importantly, because pathologists are making a specific designation as to a primary site, which may, or may not, be consistent with the clinical presentation. Most patients with CUP, however, continue to have a poor prognosis, and median survival is measured in months. Despite multiple clinical trials, a single regimen to extend both quality and quantity of life has not been identified. Doublet or triplet chemotherapy regimens (with or without a platinum agent) are commonly used with reported median survivals ranging from 4.5–13 months.[9,10,18–21]

In CUP, both liver involvement and multiple sites of disease portend a poorer prognosis.[6–8,22,23] Response rates and survival times are, therefore, influenced by the proportion of patients with these poor prognostic parameters in different studies. In 1 trial evaluating carboplatin and paclitaxel, 25% of patients had liver metastases, and only 15% of these patients had a response to treatment.[17] In a trial that evaluated a 3-drug regimen of carboplatin, paclitaxel, and etoposide, only 9 (16%) patients had hepatic involvement, and 2 of the 9 (22%) demonstrated a partial response.[19] By contrast, in our trial, more than 60% of enrolled patients had hepatic involvement and 30% had $\geq$3 sites of disease at presentation. Despite these poor prognostic parameters, the response rate in the subgroup of patients with liver metastases was 40%. These differences in patient characteristics between trials are likely reflective of the heterogeneity of CUP.

Autopsy series in patients with CUP have suggested that if a primary is identified, up to 50% of the time it is of lung, pancreatic, or hepatobiliary origin.[3,24] If lung cancer is suspected clinically, carboplatin and paclitaxel with or without etoposide, may be a reasonable treatment option.[16,17,19] However, if the primary is suspected to have originated below the diaphragm or there is significant liver involvement, then carboplatin and paclitaxel may be less favored, and a fluoropyrimidine or gemcitabine-based treatment may be more effective.

The combination of gemcitabine, carboplatin, and capecitabine was generally well tolerated despite the occurrence of cytopenias frequently observed in the first cycle. Greater toxicity was also noted in patients with a baseline PS of 2. In those patients, an initial dose reduction of 20% for all 3 agents must be considered. It should be noted that granulocyte growth-factor support was not routinely used in this trial. Although myeloid growth factors would likely ameliorate neutropenia, they may exacerbate thrombocytopenia, which was also dose limiting with this regimen. In addition, the protocol specified full-dose gemcitabine to be administered on Day 8 for a platelet count above 75,000, which, in combination with carboplatin, led to subsequent platelet nadirs that were under acceptable limits. Alternative scheduling or dosing of carboplatin or substitution with oxaliplatin should be investigated to address the concern of myelosuppression.

It may be noted that there is a close approximation of the progression-free survival curve to the overall-survival curve. In patients with progressive disease, 19 (68%) patients received subsequent chemotherapy with little benefit, further demonstrating the limitations of present treatment options. The majority (57%) of the 14 patients who did not receive second-line therapy had a Zubrod performance status of 2 at study entry, which precluded additional treatment that could have had an impact on their overall survival.

In the near future, molecular characterization of CUP may identify a primary origin of the cancer or determine sensitivity and resistance profiles to guide systemic treatment. Unfortunately, benefits of systemic therapy for advanced primary malignancies of the lung, pancreas, and hepatobiliary system are limited, so the identification of 1 of these sites as the site of origin of CUP is not likely to affect prognosis. Despite this, our study seems to indicate that the 3-drug regimen of carboplatin, gemcitabine, and cape-

citabine is active against CUP and should be considered a reasonable option for therapy, particularly for those patients with hepatic involvement. Ultimately, molecular identification and classification of these tumors will open opportunities to treat patients with targeted agents tailored specifically to the molecular make-up of an individual patient' malignancy.

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