The Efficacy of Epirubicin, Cisplatin, Uracil/Tegafur, and Leucovorin in Patients with Advanced Biliary Tract Carcinoma

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BACKGROUND. Advanced biliary tract carcinoma is among the most prevalent fatal diseases in Korea. However, to our knowledge, to date no effective therapeutic modality has been shown to prolong the survival of patients in the inoperable stages of this disease.

METHODS. This Phase II study was conducted to determine the efficacy and toxicity of a combined regimen of epirubicin, cisplatin, and uracil/tegafur (UFT) modulated by leucovorin in patients with advanced or recurrent biliary tract carcinoma.

RESULTS. Eleven of 40 patients (27.5%) had gallbladder carcinoma, and the remaining patients had tumors arising from other sites in the biliary tract. All patients were treated with intravenous epirubicin (50 mg/m^2 on Day 1), intravenous cisplatin (60 mg/m^2 on Day 1), oral UFT (300 mg/m^2 per day on Days 1–21), and oral leucovorin (75 mg per day on Days 1–21). Nine patients exhibited a partial response, representing 22.5% of the possible response rate (95% confidence interval [95% CI], 12.8–32.2%) based on an intention-to-treat analysis. The median survival was 34 weeks (95% CI, 20–48 weeks), and the median time to disease progression was 16 weeks (95% CI, 7–25 weeks). Neutropenia and thrombocytopenia comprised dose-limiting toxicity conditions.

CONCLUSIONS. The combination of epirubicin, cisplatin, and UFT modulated by leucovorin was active marginally in patients with advanced biliary tract carcinoma and was capable of stabilizing the disease effectively. Because it was a safe and convenient treatment modality, it may be used in outpatient care with only minor toxicity in patients with advanced malignancies of the biliary tract. ***Cancer*** **2005; 103:2338–43.** *© 2005 American Cancer Society.*

KEYWORDS: biliary tract carcinoma, chemotherapy, epirubicin, uracil plus tegafur (UFT).

Hepatobiliary tract malignancies are the fifth leading cause of cancer-related deaths in Korea. Although complete surgical resection is the only actual curative treatment, the prognosis remains dismal, because most patients seek treatment only when they have disease in advanced stages or after their disease has reached inoperable morbid status. The median survival of patients with inoperable biliary tract carcinoma has been reported as < 4 months.[1] In addition, surgical procedures are challenging technically; thus, the local failure rate with respect to disease control remains quite high.[2] To improve prognosis and to achieve better quality of life for patients with this disease, the development of effective chemotherapy is essential.[3] However, to our knowledge, to date no single agent or combination regimen of chemotherapeutic agents has demonstrated the ability to

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prolong survival or improve quality of life in patients with biliary tract carcinoma.[4]

5-Fluorouracil (5-FU) has constituted the basis of previous chemotherapy regimens for the treatment of biliary tract carcinoma. When it was used as a single agent, 5-FU achieved a response rate of 10–20%,[5] and bolus 5-FU administration modulated by leucovorin resulted in a response rate of 32.1%.[6] Thus, intravenous 5-FU infusion has been the preferred method in previous studies.[3,7–9] Because the combined regimen of epirubicin, cisplatin, and 5-FU as a protracted infusion (CEF therapy) was reported as effective first in patients with gastroesophageal carcinoma,[10] this combination was attempted in patients with biliary tract carcinoma, and a positive response rate of 40% was reported.[8] However, this therapy required both implantable vascular access and an infusion pump, limiting its use to inpatient-based treatment.

Oral chemotherapeutic agents can be used more comfortably than other forms of delivery. Uracil plus tegafur (UFT) is the oral prodrug form of 5-FU. It combines uracil and tegafur in a 4:1 ratio, and tegafur is converted to 5-FU by in vivo metabolism. It has been reported that long-term oral administration of UFT was as effective as intravenous 5-FU.[11,12] Based on these results, we modified the CEF regimen, replacing the 5-FU intravenous infusion with oral UFT, and included leucovorin to moderate the antitumor effects of UFT. Thus, we designed a study for the evaluation of the synergistic effects epirubicin and cisplatin with oral UFT moderated by leucovorin. In this Phase II study, we determined both the efficacy and toxicity of combination chemotherapy with epirubicin, cisplatin, and oral UFT moderated by leucovorin in patients with inoperable, advanced biliary tract carcinoma.

MATERIALS AND METHODS

Patients

Patients in this study were referred to the Oncology/Hematology Division of the Korea University Medical Center (Seoul, Korea) between May 2000 and July 2004. They were required to have histologically and/or cytologically confirmed biliary tract carcinomas that initially were inoperable or to have recurrent bile duct or periampullary carcinomas after surgical resection. Other eligibility criteria for this study were as follows: 1) an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, 2) age between 18 years and 75 years, 3) life expectancy ≥ 2 months, 4) serum creatinine ≤ 177 μmol, 5) adequate bone marrow reserve (neutrophil count $\geq 1500 \times 10^6$/L and platelet count $\geq 100 \times 10^9$/L/m^2), 6) at least 1 measurable lesion, and 7) informed consent for treatment. Patients with hyperbilirubinemia due to biliary obstruction were decompressed adequately by internal stenting or through the percutaneous transhepatic drainage approach. Their serum total bilirubin level had to be equal to or less than twice the upper limit of the institutional normal level.

Treatment

Epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) were administered intravenously on the first day of each cycle at the hospital, whereas UFT and leucovorin were administered orally from Day 1 to Day 21 on an outpatient basis. UFT was administered at a dose of 300 mg/m^2 per day, and leucovorin was administered at a dose of 75 mg/day, with both drugs given as 3 divided doses. This treatment was repeated every 4 weeks. Chemotherapy was continued until either the progression of disease or unacceptable toxicity ensued. Patient compliance for UFT was verified by counting the remaining pills or by interviews at the end of each course of treatment. The administration of UFT was withheld in patients with Grade 3 or greater mucositis, nausea/emesis, and hematologic toxicities of leukopenia and thrombocytopenia. After complete resolution of the aforementioned toxic effects, UFT treatment recommenced at the same dosage as before. In patients who had previous Grade 3–4 mucositis or diarrhea, UFT was administered at a 25% reduced dose. In addition, in patients with Grade 3 or greater hematologic toxicity, epirubicin and cisplatin were recommenced but, again, at a 25% reduced dose. Once a dose was reduced, dose reescalation was prohibited.

Evaluation of Response and Toxicity

Every two cycles of treatment, response was evaluated based on the criteria developed by the World Health Organization (WHO) as follows: a complete response was defined as the complete disappearance of all assessable lesions; a partial response was defined as a decrease $\geq$ 50% in the sum of the products of the longest tumor dimension and its greatest perpendicular dimension and no increase in the size of any other known disease; stable disease was defined as a decrease $<$ 50% or an increase $<$ 25% in tumor size; and progressive disease was defined as an increase $>$ 25% in the products of the 2 greatest dimensions of at least 1 tumor or as the development of a newly developed lesion. Contrast-enhanced spiral computerized tomography was performed to document response to treatment. On Day 1 of each cycle, serum CA 19-9, electrocardiogram, serum biochemistry, and chest X-rays were obtained, with hematologic and liver function tests performed between Days 10 and 14

TABLE 1
Clinical Characteristics of the Current Study Patients

Characteristic	No. of patients
Male:female ratio	29:11
Age (yrs)	
Median	58
Range	21–75
Performance status (ECOG)	
0–1	33
2	7
Previous treatment	
Surgery	9
Chemotherapy	2
None	29
Primary tumor sites	
Hilar or extrahepatic bile duct	17
Gallbladder	11
Peripheral bile duct	9
Ampulla of Vater	3
Sites of metastatic disease	
Liver	18
Lymph node	7
Lung	6
Bone	2
Carcinoma peritonei	2
Brain	1

ECOG: Eastern Cooperative Oncology Group.

of each cycle. Toxicities were evaluated according to WHO toxicity grade.

Statistical Analysis

The time to disease progression was calculated from the day of the first chemotherapy treatment until the day of the first documented evidence of disease progression. If a patient started additional antitumor treatment during follow-up, then the first day of the new treatment was documented as the end of response. Survival was calculated from the start of therapy to death, as established by the Kaplan–Meier method.

RESULTS

Patients

Clinical characteristics of the patients are presented in Table 1. There were 29 male patients and 11 female patients. They had an age range of 21–75 years, and the median age was 58 years. Most patients (33 of 40 patients; 82.5%) had an ECOG performance status of 0–1. Most patients (95%) were chemotherapy naïve, and 2 patients had received previous treatment with a combined regimen of gemcitabine and cisplatin. Eleven patients (27.5%) had gallbladder carcinoma, and the remaining patients exhibited tumors arising from other biliary tract areas. The liver and abdominal lymph nodes were the most common sites for metastasis. With the exception of one patient with stable disease who strongly wanted to begin second-line treatment, second-line antitumor treatment was administered to 12 patients who had documented progressive disease.

TABLE 2
Responses to Treatment: Intention-to-Treat Analysis (n = 40 patients)

Response	No. of patients	%
Confirmed response	9	22.5
Complete response	0	0.0
Partial response	9	22.5
Stable disease	9	22.5
Progressive disease	16	40.0
Not assessable	6	15.0

Responses and Survival

Thirty-four of 40 patients were evaluated in terms of their response to treatment. One patient, who was Korean-Chinese, returned to his country after one course of treatment. The remaining five patients were lost to follow-up or were excluded from the study before evaluation due either to their refusal to visit the hospital or to toxic death. No patient achieved a complete response, but 9 patients achieved a partial response, representing a 22.5% response rate (95% confidence interval [95% CI], 12.8–32.2%) based on an intention-to-treat analysis (see Table 2). Nine patients exhibited stable disease, and 16 patients had disease progression. Therefore, 18 (45%) patients achieved disease stabilization as a result of treatment. The median response duration of the 9 responding patients was 12 weeks (range, 7–24 weeks), and the disease-stabilizing effect in patients with stable disease lasted a median of 25 weeks (95% CI, 16–34 weeks). The median survival and the median time to disease progression was 34 weeks (95% CI, 20–48 weeks) and 16 weeks (95% CI, 7–25 weeks), respectively (Figs. 1, 2).

Toxicities and Dose Reductions

Of the 153 cycles of treatment (median, 3 cycles; range, 1–10 cycles), 147 cycles were assessable for toxicity. There were 2 treatment-related deaths: 1 due to Grade 4 hepatitis and the other due to febrile neutropenia. The treatment caused significant dose-limiting hematologic toxicity, and 12 of 40 patients (30%) experienced Grade 3–4 neutropenia, but only 3 of those patients exhibited febrile neutropenia. Thrombocytopenia $\geq$ Grade 3 was observed in only 2 patients during 2 courses of treatment. The most com-

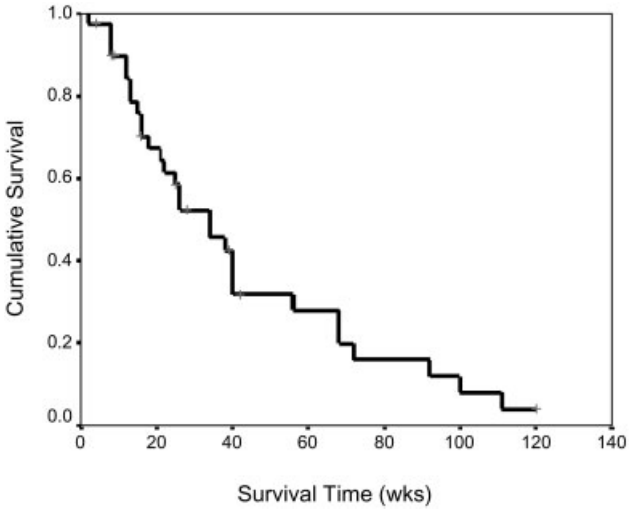

FIGURE 1. This Kaplan–Meier curve illustrates overall survival ($n = 40$ patients).

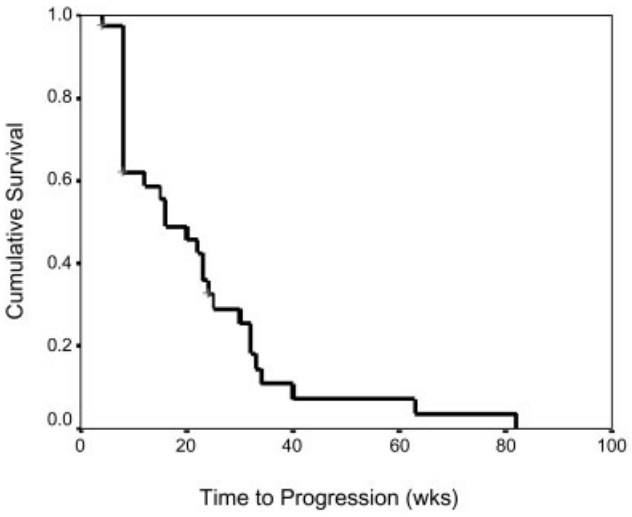

FIGURE 2. This Kaplan–Meier curve illustrates the time to disease progression ($n = 9$ patients).

mon nonhematologic toxicity was nausea and emesis, which was Grade 3–4 in 4 patients (10%), resulting in subsequent dose reductions in their UFT regimens. Diarrhea was an uncommon adverse event in the current study population and responded well to dosing delays followed by resumption of normal therapy after the diarrhea resolved. Other treatment-related side effects, including anorexia, nausea, emesis, and peripheral neuropathy, proved manageable. No significant cardiac toxicity was observed. Table 3 shows the toxicities of the 40 patients who could be assessed with regard to their adverse events after > 1 course of treatment. The dose intensity of each drug in the progressive treatment courses is shown in Figure 3.

TABLE 3
Treatment-Related Toxicity[a]

	Grade (% of cycles) ($n = 147$ cycles)		Grade (% of patients) ($n = 40$ patients)	
Toxicity	**1–2**	**3–4**	**1–2**	**3–4**
Hematologic toxicity				
Neutropenia	15 (10.0)	13 (8.8)	9 (22.5)	12 (30)
Anemia	14 (9.5)	3 (2.0)	11 (27.5)	3 (7.5)
Thrombocytopenia	14 (9.5)	2 (1.3)	10 (25)	2 (5.0)
Nonhematologic toxicity				
Alopecia	9 (6.1)	1 (0.7)	9 (22.5)	1 (2.5)
Hepatitis	3 (2.0)	2 (1.3)	3 (7.5)	2 (5.0)
Nausea/emesis	8 (5.4)	4 (2.7)	8 (20)	4 (10)
Diarrhea	4 (2.7)	2 (1.3)	4 (10)	2 (5.0)
Anorexia	—	1 (0.6)	—	1 (2.5)
Stomatitis	1 (6.8)	—	1 (2.5)	—
Peripheral neuropathy	1 (6.8)	—	1 (2.5)	—

[a]Grading of toxicities was performed according to World Health Organization criteria.

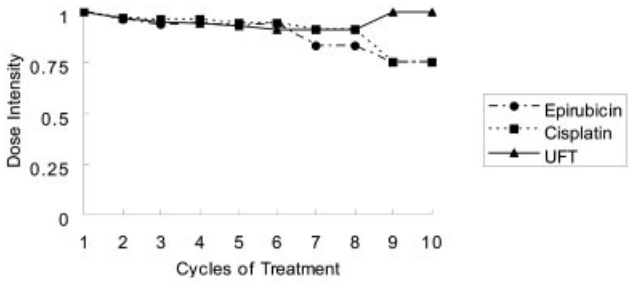

FIGURE 3. The mean dose intensities are illustrated for epirubicin, cisplatin, and uracil plus tegafur in a 4:1 ratio (UFT).

DISCUSSION

In this study, we achieved a 22.5% response rate (95% CI, 12.8–32.2%), with an additional 22.5% of patients achieving disease stability based on an intention-to-treat analysis. Therefore, epirubicin, cisplatin, and UFT modulated by leucovorin stabilized these aggressive tumors in 45% of the patients treated. Continuous-infusion 5-FU with cisplatin and epirubicin (CEF therapy) has been reported as effective in gastrointestinal carcinomas, particularly gastroesophageal carcinoma.[10] To our knowledge, two reports have been published to date regarding this combined regimen in patients with biliary tract malignancies: A British study that included 20 evaluable patients reported a response rate of 40% with tolerable hematologic toxicity.[8] The other, more recent study, which was conducted in Japan, reported marginal activity (19%) against biliary tract carcinomas that was associated with significant hematologic toxicity.[13] Theoretically,

those two previous studies did not differ significantly in terms of response rates, because their 95% confidence intervals overlapped. Moreover, if the response rate from the British study were analyzed based on an intention-to-treat analysis, then it would correspond to a response rate of 32%. Most differences in adverse events between the two studies may be attributable to the cisplatin dosage (80 mg/m^2), which was 33% higher in the Japanese study than in the British study. Based on those studies, we chose cisplatin at a dose of 60 mg/m^2 to investigate its potential synergistic effect with epirubicin and UFT. This resulted in a much lower incidence of Grade 3–4 neutropenia (70% vs. 30%) compared with what was reported in the Japanese study.

UFT, which is a second-generation oral 5-FU prodrug, is used commonly, largely due to its good pharmacokinetics, which are similar to protracted intravenous injections of fluorouracil but with better toxicity profiles.[14] In addition, UFT did not require intravenous access device and, thus, clearly was much more convenient. Previous studies with UFT modulated by leucovorin in biliary carcinomas were unsatisfactory in terms of efficacy but also were not associated with obvious toxicity.[15,16] However, when combined with other chemotherapeutic agents, the efficacy and feasibility of UFT in the treatment of patients with biliary tract malignancies still have not been investigated. Our study constitutes the first report demonstrating the synergistic effects of UFT modulated by leucovorin with epirubicin and cisplatin as a treatment for biliary tract carcinoma. In addition, the results of this study demonstrate that UFT can be administered on an outpatient basis, thereby improving quality of life compared with the 5-FU administration protocol but without compromising its efficacy.

With regard to toxicity, our treatment regimen caused significant hematologic toxicity, which was the most frequent cause of dose reduction. Although two patients died of neutropenia with septic shock and hepatitis, this treatment essentially was tolerated well. Grade 3–4 neutropenia was observed in 12 patients (30%), corresponding to 8.8% of total treatment courses. However, subsequent dose modifications of epirubicin and cisplatin prevented the occurrence of serious neutropenia, allowing further treatment cycles. Compared with the hematologic toxicities reported in a previous Japanese study that used cisplatin at a dose of 80 mg/m^2, our treatment regimen appeared safer.[13] Two deaths were observed after the first course of treatment, including one that was caused by hepatitis and one that was caused by septic shock with febrile neutropenia. Surprisingly, gastrointestinal toxicities, such as oral mucositis or diarrhea, were not observed with significant frequency in the population studied. A reduction in the dosage of UFT was warranted in only 2 patients due to gastrointestinal toxicities $\geq$ Grade 3. Compared with the previous study regarding CEF therapy using infusional 5-FU, stomatitis and diarrhea were much less frequent with our UFT treatment.[8] Therefore, the current study data suggest that UFT can be used in the treatment of patients with advanced biliary tract carcinoma to replace the infusional 5-FU, resulting in a better safety profile and increased convenience.

In the current study, we were unable to assess response in six patients due to their early withdrawal from the study after the first course of treatment. In addition to the two patients with treatment-related mortality, three patients had to discontinue treatment and were lost to follow-up due to rapid disease progression rather than intolerance to treatment. All of the patients who withdrew early initially had a performance status of 1. In addition, among seven patients who had a performance status of 2,there were two patients who responded to treatment. This result is in disagreement with the conclusions of a recent report based on Japanese Phase II trials, which concluded that patients with a performance status of 2 who had gallbladder carcinoma may not benefit from chemotherapy.[17] With regard to the primary disease site, several reports have asserted that patients with gallbladder carcinoma respond more readily to chemotherapy compared with patients who have disease at other sites. In this study, we found no difference in the response rates according to primary tumor site. Therefore, further careful study will be required to ascertain which patients with biliary tract carcinomas will tend to benefit from chemotherapy.

The combination of epirubicin, cisplatin, and UFT modulated by leucovorin appears to be marginally active and effectively stabilizes advanced biliary tract carcinoma. Considering its safety and convenience, we can use this regimen in outpatient care with only minor complications from toxicity.

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