all response rate of 33.3 (95% confidence interval, 13.3–59.0%). No change was noted in 9 patients (50%) and progressive disease in 3 patients (16.7%). The mean response duration was 4.8 months (range 2.8–15.9). The serum CA 19-9 level was reduced to less than half from baseline values in 8 (61.5%) of the 13 patients who had a pretreatment level greater than the upper limit of normal (37 U/ml). At the time of analysis, 9 patients had died because of disease progression. The median progression-free and the median overall survival times were 5.0 and 7.6 months, respectively.

Discussion

To improve the prognosis of patients with advanced pancreatic cancer, gemcitabine-based combination chemotherapy has been actively investigated, although many phase III trials have failed to demonstrate any survival benefit of combination chemotherapy in comparison with gemcitabine as a single agent. 5-FU has been selected as a candidate to be investigated in combination with gemcitabine in patients with pancreatic cancer because of its favorable toxicity profile and modest but substantial activity in this disease. Gemcitabine is considered to enhance the effect of the 5-FU metabolite 5-FdUMP by reducing the concentration of its physiological competitor via inhibition of ribonucleotide reductase [24]. Preclinical studies have demonstrated synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells [25, 26]. Clinical studies have reported activity of gemcitabine in pancreatic cancer patients with refractoriness to 5-FU [27], suggesting the lack of cross-resistance between the two agents. Several phase I and II studies of combination therapy with gemcitabine and 5-FU for advanced pancreatic cancer have demonstrated relatively good response rates of around 20% with acceptable toxicity profiles [14–18]. A phase III study comparing gemcitabine alone with gemcitabine plus weekly bolus 5-FU showed that median progression-free survival was significantly longer in the combination arm compared with gemcitabine alone (3.4 vs. 2.2 months, $p = 0.022$); however, median overall survival was not significantly prolonged (6.7 vs. 5.4 months, $p = 0.09$) [5].

The novel oral anticancer agent S-1 was developed to improve the tumor-selective toxicity of 5-FU and has shown efficacy in a variety of solid tumors, including pancreatic cancer [9–13]. With the aim of developing a more effective chemotherapeutic regimen for pancreatic cancer, we decided to conduct a clinical study of combination therapy with gemcitabine and S-1. Since this combination has not previously been investigated, a phase I study was carried out to determine MTD and DLT.

In the present study, MTD was not reached because only 2 of the 6 patients experienced DLT at the highest dose, level 4. Although the 6 patients at level 4 have received a total of 34 cycles of treatment (average 5.7, range 2–12), there was no indication of cumulative toxicity. Therefore, dose level 4 (gemcitabine 1,000 mg/m^2/week, S-1 80 mg/m^2/day) was considered the recommended dose in further studies of this combination regimen. Because 2 of the 6 patients experienced DLT at this level, it goes without saying that more large-scale studies will be necessary to confirm the safety of our recommended dose. The overall toxicity of this regimen was mild, and neither unexpected nor life-threatening toxicities were observed during the study, indicating that S-1, like other fluoropyrimidines, can be safely combined with gemcitabine.

Neutropenia was the major DLT of this combination regimen: 1 of the 6 patients at dose level 3, and 2 of the 6 patients at dose level 4, experienced grade 4 neutropenia. Neutropenia as the DLT was to be expected because myelosuppression, especially neutropenia, is one of the most common toxicities of each individual drug. The neutrophil nadir typically occurred on day 15, but in most cases, the neutrophil count spontaneously recovered to baseline values within a week. Furthermore, no febrile neutropenia was observed during any of the 125 cycles of treatment, suggesting that the myelosuppression caused by this combination regimen is manageable on an outpatient basis.

The non-hematological toxicities commonly observed with our regimen were gastrointestinal toxicities such as nausea and anorexia. Although 1 patient at dose level 2 experienced transient grade 3 nausea and grade 3 anorexia, no DLTs associated with gastrointestinal toxicities were observed. Diarrhea was also mild and rare in the current study, similar to previous reports from Japanese studies of single-agent S-1; however, relatively severe diarrhea induced by S-1 has been reported in studies from Europe and the United States [28–30]. For example, Hoff et al. [28] reported that severe diarrhea occurred in all of the 3 patients who received S-1 at a dose of 40 mg/m^2 b.i.d. It is not clear why the toxicity profile and MTD of S-1 in Western studies differ from those in studies with Japanese populations, although a pharmacokinetic study suggested that the conversion of tegafur to 5-FU may occur more slowly in Japanese patients than in patients from other ethnic groups [31]. In any event, it may be dangerous to apply the results of our study directly to

treatment of Western patients, particularly from the viewpoint of gastrointestinal toxicity.

In the present study, 11 (61.1%) of the 18 patients experienced grade 1 or greater rash. This toxicity was mild and manageable, although 1 patient at dose level 4 developed grade 3 rash, requiring temporary treatment discontinuation. The reason for the enhanced cutaneous toxicity during combination therapy with gemcitabine and S-1 is unknown, although cutaneous toxicity has already been reported in patients receiving gemcitabine and 5-FU combination regimens. Hidalgo et al. [14] reported grade 1 or greater cutaneous toxicity in 11 (42.3%) of the 26 patients in a phase I–II study with gemcitabine and 5-FU. One of these patients developed a severe cutaneous reaction, manifested as generalized exfoliative dermatitis, after the first cycle of chemotherapy.

Combination therapy with gemcitabine and S-1 was associated with promising activity in advanced pancreatic cancer. Six (33.3%) of the 18 patients achieved an objective response. Of the 13 patients who had a pretreatment serum CA 19-9 level greater than 37 U/ml, the CA 19-9 level decreased more than 50% in 8 patients (61.5%). In addition, the median progression-free survival time of 5.0 months and the median overall survival time of 7.6 months are encouraging. These efficacy data in this study, which compare favorably with those reported for single-agent gemcitabine, support further studies of this regimen.

In conclusion, our combination regimen of gemcitabine and S-1 was well tolerated up to dose level 4. The major toxicities were myelosuppression, gastrointestinal toxicity and skin rash, although most of these toxicities were mild and reversible. Six of the 18 patients showed a partial response, suggesting a promising antitumor activity of this regimen against pancreatic cancer. A multicenter phase II study of this regimen, 1,000 mg/m^2/week gemcitabine on days 1 and 8 and 80 mg/m^2/day S-1 from days 1 to 14 every 3 weeks, is under way in patients with metastatic pancreatic cancer.

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A Phase II Trial of Continuous Infusion of 5-Fluorouracil, Mitoxantrone, and Cisplatin for Metastatic Hepatocellular Carcinoma

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BACKGROUND. The aim of the current study was to evaluate the antitumor activity and toxicity of continuous infusion of 5-fluorouracil, mitoxantrone, and cisplatin (FMP therapy) in chemotherapy-naive patients with metastatic hepatocellular carcinoma (HCC).

METHODS. Fifty-one patients with metastatic HCC who had not undergone previous systemic chemotherapy were enrolled. The therapy consisted of intravenous administration of 80 mg/m^2 cisplatin and 6 mg/m^2 mitoxantrone on Day 1 and continuous intravenous infusion of 450 mg/m^2 5-fluorouracil per day on Days 1–5. The treatment was repeated every 4 weeks for a maximum of 6 courses with dose adjustments based on the observed toxic effects if there was no evidence of tumor progression or unacceptable toxicity.

RESULTS. Of the 51 enrolled patients, 14 (27%) achieved a partial response (95% confidence interval, 16–42%) with a median duration of 7.6 months (range, 2.3–18.4 months). Twenty-seven patients (53%) showed no change and 9 (18%) had progressive disease. The median survival time, 1-year survival rate, and median progression-free survival time for all patients were 11.6 months, 44.3%, and 4.0 months, respectively. The main Grade 3 and 4 toxicities were leukocytopenia (67%), neutropenia (71%), thrombocytopenia (27%), and elevated levels of aspartate aminotransferase (37%) and alanine aminotransferase (41%). These symptoms were generally brief and reversible, with the exception of one treatment-related death due to acute hepatic failure.

CONCLUSIONS. FMP therapy had significant antitumor activity with acceptable toxicity in patients with metastatic HCC. *Cancer* **2005;103:756–62.**

KEYWORDS: hepatocellular carcinoma, chemotherapy, metastasis, 5-fluorouracil, mitoxantrone, cisplatin.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. It is highly prevalent in Africa and Asia, and in recent years, its incidence has been increasing in Western countries. Although a range of therapeutic options are available, the efficacy of these methods remains unsatisfactory and the prognosis of patients with HCC is still poor.[1–3] Curative therapies, such as hepatic resection and liver transplantation, are applicable to only a small group of patients because of poor liver function, metastasis, or both. Local treatments, such as percutaneous ethanol injection, radiofrequency ablation, or transcatheter arterial embolization, have been reported to be useful for treating patients with unresectable disease. Unfortunately, however, in most patients with HCC, the disease progresses to an advanced stage for which effective local treatment is

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not available.[1–3] Currently, patients with HCC at this stage generally undergo chemotherapy, but this has limited value in clinical practice. The activity of single agents is limited, with only a few drugs achieving a response rate > 10%. Moreover, combination chemotherapy has proven equally disappointing because it rarely results in any meaningful clinical improvement.[1–23] Thus, despite decades of trials of various agents, no chemotherapeutic drug has shown sufficient efficacy to be acknowledged as a standard therapy. Therefore, an effective chemotherapy regimen is a much sought after goal.

Mitoxantrone is a synthetic anthraquinone, with antitumor activity against human tumor cell lines and animal models of leukemia comparable and often superior to that of doxorubicin.[4] Clinical trials of this drug have demonstrated moderate activity against HCC with a lower incidence of adverse effects, such as hematologic and cardiac toxicity, than other chemotherapeutic agents.[5–8] Cisplatin has a broad spectrum of antineoplastic activity, and there have been several reports demonstrating favorable effects of this agent on HCC.[8,9] Between the two drugs, significant therapeutic synergism has been observed against other malignancies, although the mechanism has not been elucidated fully.[4] The pyrimidine antimetabolite, 5-fluorouracil (5-FU), was the first reported chemotherapeutic agent to be used in the treatment of HCC, and there has been much interest in the possibility of increasing 5-FU activity[10–16] and therapeutic selectivity with so-called modulators such as cisplatin.[17,18] In clinical trials, combination chemotherapy including 5-FU and cisplatin has demonstrated high response rates in patients with HCC.[17,18] Therefore, we conducted a Phase II trial to evaluate the antitumor activity and toxicity of the systemic chemotherapy regimen of 5-FU, mitoxantrone, and cisplatin (FMP therapy) in patients with metastatic HCC.

MATERIALS AND METHODS

Eligibility

Patients eligible for study entry had HCC with extrahepatic metastases. The diagnosis was made by either histologic examination or typical computed tomographic scans, angiographic findings, and elevated serum α-fetoprotein levels (AFP). Eligibility criteria included the following factors: age 20–74 years; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2; bidimensionally measurable disease; an estimated life expectancy $\geq$ 8 weeks after study entry; no previous systemic chemotherapy excluding chemoembolization; adequate hematologic function (hemoglobin level $\geq$ 10 g/dL, leukocyte count $\geq$ 3000 cells/mm^3, neutrophil count $\geq$ 1500 cells/mm^3, and platelet count $\geq$ 70,000 cells/mm^3); adequate hepatic function (serum total bilirubin level $\leq$ 2.0 mg/dL, serum albumin level $\geq$ 3.0 g/dL, and serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels $\leq$ 200 IU/L); adequate renal function (serum creatinine level within normal limits and creatinine clearance $\geq$ 60 mL per minute); and written informed consent. Patients with tumor thrombosis in the main portal trunk were excluded, because such patients have a reportedly poor prognosis and tumor response to systemic chemotherapy.[24–27] Previous local therapy for intrahepatic lesions before this treatment, such as hepatic resection, percutaneous local ablation, or transcatheter arterial chemoembolization, was allowed if it had not been done within the previous 4 weeks. Bone metastases were not regarded as measurable lesions.

The exclusion criteria were active infection, severe heart disease, refractory pleural effusion or ascites, known metastases to the central nervous system, severe mental disorder or encephalopathy, active gastroduodenal ulcer or esophageal bleeding within 1 month, active concomitant malignancy, pregnant and lactating females, females of childbearing age unless using effective contraception, and other serious medical conditions.

Pretreatment evaluation included a complete history and physical examination. The laboratory procedures were a complete differential blood count, biochemistry tests, viral markers including serum hepatitis B surface antigen (HBsAg) and serum hepatitis C virus (HCV) antibody, urinalysis, and tumor markers including serum levels of AFP and protein induced by vitamin K absence or antagonist-II (PIVKA II). All patients underwent electrocardiography, chest radiography, gastroscopy, and computed tomography (CT) scans within 4 weeks before chemotherapy. HCC was diagnosed by histologic examination or distinctive findings of CT scans and/or angiography.

Treatment Schedule

All eligible patients were treated with the FMP regimen. 5-FU was administered as a continuous intravenous infusion at a dose of 450 mg/m^2 on Days 1–5. Mitoxantrone was administered as an intravenous infusion at a dose of 6 mg/m^2 on Day 1. Cisplatin was administered as an intravenous infusion at a dose of 80 mg/m^2 over a 2-hour period on Day 1 with standard hydration. In subsequent courses, the dose of each drug was adjusted to the toxicities observed. For example, patients who had experienced Grade 4 hematologic toxicities or Grade 3 neutropenia and/or leukocytopenia with high fever ($\geq$ 38 °C) received 4 mg/m^2 mitoxantrone, patients who had experienced

Grade 3 or 4 stomatitis, diarrhea, and/or hand–foot syndrome received 400 mg/m^2 5-FU, patients who had experienced Grade 3 or 4 elevated levels of serum creatinine and/or creatinine clearance < 40 mL per minute did not receive cisplatin. Antiemetics including 5-HT4 receptor antagonist and dexamethasone were administered prophylactically. Granulocyte colony-stimulating factor was given when neutropenia and/or leukocytopenia of Grade 3/4 with high fever (≥ 38 °C) were observed. If there was no evidence of tumor progression or unacceptable toxicity, the treatment was repeated every 4 weeks until a maximum of 6 courses were achieved. Patients who were refractory to this regimen were allowed to receive other anticancer treatment at their physician's discretion.

Response and Toxicity Evaluation

The objective tumor response was assessed by CT scan every 4 weeks after the beginning of FMP therapy. Response and toxicity were evaluated according to World Health Organization guidelines.[28] The best overall response was recorded for each patient. During this treatment, a complete differential blood count, serum chemistry profile, and urinalysis were undertaken at least weekly. Serum AFP and PIVKA II levels were measured every 4 weeks. Disease progression-free survival (PFS) was defined as the time from the date of initial treatment to first documentation of disease progression or death. The duration of response was defined as the interval from the onset of a partial response (PR) to the first evidence of disease progression or death. Overall survival was measured from the date of initial treatment to the date of death or the date of last follow-up.

Statistical Design

The primary end point of the current study was the efficacy and toxicity of this regimen, and the secondary end point was survival and disease PFS. The number of patients to be enrolled was planned using a 2-step design[29] based on the assumptions that the expected response rate was 30%, the response rate judged as no activity was 15%, the α error was 10%, and the β error was 10%. An interim analysis was planned after 25 patients had been enrolled. If 1 or 2 of the first 25 patients had a PR or complete response (CR), the study was to be ended. If a response was detected in > 2 of the first 25 patients studied, an additional 25 patients were to be studied in a second stage of accrual to estimate more precisely the actual response rate. This population was defined as including any patients who received at least one course of study medication. The survival time and the disease PFS were calculated by the Kaplan–Meier method.[30]

TABLE 1
Patient Characteristics

Characteristics	No. of patients (%)
Median age (range)	61 (34–74 yrs)
Gender	
Male	47 (92)
Female	4 (8)
ECOG performance status	
0	43 (84)
1	8 (16)
History of blood transfusion	
Positive	10 (20)
Alcohol abuse[a]	
Positive	12 (24)
Hepatitis B surface antigen	
Positive	20 (39)
Hepatitis C virus antibody	
Positive	27 (53)
Previous treatment	
Hepatic resection	35 (69)
Percutaneous local ablation	10 (20)
Transcatheter arterial chemoembolization	30 (59)
None	7 (14)
Child–Pugh stage	
A	*45 (88)*
B	*6 (12)*
Organs affected by metastases	
Lung	36 (71)
Lymph nodes	24 (47)
Bone	7 (14)
Adrenal gland	4 (8)
Peritoneum	2 (4)
Median CLIP score (range)	2 (0–5)
Median α-fetoprotein level (ng/dL) (range)	190 (3–509,500)
Median PIVKA II level (mAU/mL) (range)	1420 (10–185,200)

ECOG: Eastern Cooperative Oncology Group; CLIP: Cancer of the Liver Italian Program; PIVKA II: protein induced by vitamin K absence or antagonist-II.
[a] Ethanol intake ≥ 80 g per day for ≥ 5 years.

This Phase II trial was approved by the institutional review board of the National Cancer Center (Tokyo, Japan).

RESULTS

Patient Characteristics

Fifty-one patients were enrolled between September 1993 and January 2003 at the National Cancer Center Hospital. The diagnosis of HCC was confirmed by histologic examination in 45 patients (88%). In the remaining 6 patients (12%), diagnosis was based on typical CT scan findings, angiographic findings, and elevated serum AFP levels. The characteristics of the patients are listed in Table 1. There were 47 males and 4 females with a median age of 61 years (range, 34–74 years). HBsAg and HCV antibody were positive in 20 patients (39%) and 27 patients (53%), respectively. All

TABLE 2
Toxicity

Characteristics	Grade (WHO criteria)			
	1 (%)	2 (%)	3 (%)	4 (%)
Hematologic toxicity				
Leukocytopenia	3 (6)	14 (27)	28 (55)	6 (12)
Neutropenia	2 (4)	12 (24)	15 (29)	21 (41)
Anemia	15 (29)	13 (25)	2 (4)	0 (0)
Thrombocytopenia	9 (18)	16 (31)	12 (24)	2 (4)
Nonhematologic toxicity				
Nausea/emesis	27 (53)	10 (20)	6 (12)	0 (0)
Stomatitis	17 (33)	2 (4)	1 (2)	0 (0)
Diarrhea	6 (12)	2 (4)	0 (0)	0 (0)
Hiccup	24 (47)	2 (4)	0 (0)	0 (0)
Fatigue	27 (53)	5 (10)	5 (10)	0 (0)
Sensory neuropathy	5 (10)	0 (0)	0 (0)	0 (0)
Alopecia	13 (25)	17 (33)	0 (0)	0 (0)
Skin rash	3 (6)	0 (0)	0 (0)	0 (0)
Hand-foot syndrome	0 (0)	0 (0)	0 (0)	0 (0)
Elevated total bilirubin level	24 (47)	3 (6)	1 (2)	1 (2)
Elevated Aspartate aminotransferase level	12 (24)	12 (24)	10 (20)	9 (18)
Elevated Alanine aminotransferase level	15 (29)	11 (22)	11 (22)	10 (20)
Elevated alkaline phosphatase level	13 (25)	2 (4)	1 (2)	0 (0)
Elevated creatinine level	8 (16)	0 (0)	0 (0)	0 (0)
Elevated blood urea nitrogen level	12 (24)	1 (2)	0 (0)	0 (0)

WHO: World Health Organization.

patients showed had a good ECOG performance status score of 0–1. There were 45 (88%) and 6 (12%) patients with Child–Pugh Stage A and B,[31] respectively. The major sites of extrahepatic metastases were the lungs (n = 36 [71%]) and the lymph nodes (n = 24 [41%]). The median Cancer of the Liver Italian Program (CLIP) score was 2 (range, 0–5).[32] The median serum AFP and PIVKA II levels were 190 ng/dL (range, 3–509,500 ng/dL) and 1420 mAU/mL (range, 10–185,200 mAU/mL), respectively.

A total of 150 courses were given, with a median of 2 courses (range, 1–6 courses) per patient. The reasons for treatment discontinuation were completion of treatment (6 courses) in 9 patients (18%), disease progression in 36 patients (71%), refusal of treatment in 5 patients (10%), and treatment-related death in 1 patient (2%).

Response

Fifty patients were evaluable for response. The remaining one patient could not be evaluated because of treatment-related death. No patient achieved a CR. Fourteen patients achieved a PR, giving an overall response rate of 27% (95% confidence interval, 16–42%), and the median duration of response was 7.6 months (range, 2.3–18.4 months). Twenty-seven patients (53%) showed no change and the remaining 9 (18%) had progressive disease. Two patients with a PR underwent surgical resection for residual HCC lesions after six courses of this chemotherapy regimen. These resections were successful and both patients achieved complete clinical remission of disease after surgery.

During the treatments, the serum AFP level was reduced by > 50% in 6 of 28 (21%) patients who had shown a pretreatment level of ≥ 100 U/mL, and the serum PIVKA II level was reduced by > 50% in 21 of 36 (58%) patients who had a pretreatment level of ≥ 100 mAU/mL.

Toxicity

The toxicities observed in the 51 enrolled patients are listed in Table 2. The toxicity represents the maximum grade per patient for the entire course of therapy. One patient died of acute hepatic failure due to neutropenic sepsis on Day 22 of the first course of treatment. Grade 4 leukocytopenia and neutropenia occurred in 6 (12%) and 21 (41%) patients, respectively, but both were generally brief and reversible. Thrombocytopenia and anemia were infrequent and mild. Except for one patient whose death was treatment related, even those who had pancytopenia before treatment tolerated this treatment hematologically.

Elevated AST and ALT levels were frequent nonhematologic adverse effects. Grade 3–4 toxicities were

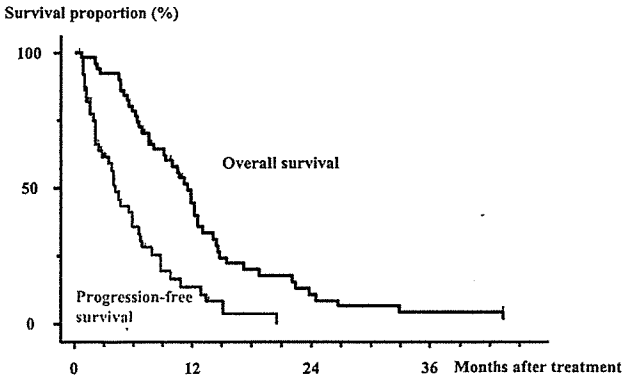

FIGURE 1. Overall survival and disease progression-free survival curves of 51 patients who received 5-fluorouracil, mitoxantrone, and cisplatin therapy for metastatic hepatocellular carcinoma. Tick marks indicate censored patients.

observed as elevated AST levels in 19 patients (37%) and elevated ALT levels in 21 patients (41%), although it was difficult to differentiate between hepatic toxicity and exacerbation of viral hepatitis. These toxicities returned to baseline levels within 1 month, and the patients were able to continue chemotherapy without dose reduction. Grade 3–4 total bilirubin elevation occurred in 2 patients (4%), 1 of whom died of acute hepatic failure due to neutropenic sepsis. However, all patients, except the 1 patient whose death was treatment related, recovered to the initial levels within 1 month without any additional treatment. There were no other serious nonhematologic toxicities.

Dose reductions according to the protocol were required in 22 patients (43%): mitoxantrone dose, 22 patients; 5-FU dose, 2 patients; and cisplatin dose, no patients.

Survival

All enrolled patients were included in the survival assessment. At the time of the analysis, 47 patients had died. The causes of death were tumor progression ($n = 40$), hepatic failure ($n = 3$), rupture of esophageal varices ($n = 1$), cerebral bleeding from brain metastasis ($n = 2$), and treatment-related death ($n = 1$). The median survival time, 1-year survival rate, and median disease PFS time for all patients were 11.6 months, 44.3%, and 4.0 months, respectively (Fig. 1). The median survival times of patients with Child–Pugh Stage A and Stage B disease were 13.2 and 6.4 months, respectively. The median survival times of patients with CLIP scores of 0–2 and 3–5 were 13.6 months and 8.1 months, respectively.

DISCUSSION

Systemic chemotherapy for unresectable HCC remains an important modality of treatment, because not all patients are suitable for effective local treatments such as surgical resection, intraarterial treatment, or local ablative therapy.[1–3] However, it has only limited value in clinical practice, because only a few patients who undergo systemic chemotherapy obtain meaningful palliation and the toxicity of chemotherapy often outweighs its benefits. Furthermore, there has been no convincing evidence so far from prospective randomized trials to suggest that systemic chemotherapy prolongs survival in comparison to no treatment.[1–3] Therefore, it remains mandatory to explore novel therapeutic strategies to improve the response and survival of patients with advanced HCC.

The possible explanations for the lack of response of HCC to anticancer agents are tumor heterogeneity, inducible overexpression of the multidrug resistance gene, and/or inherent resistance by an unexplained mechanism.[1–3] Therefore, combination therapy is considered to be more effective than monotherapy. In the current study, we chose three anticancer agents with synergic effects (i.e., 5-FU, mitoxantrone, and cisplatin). In the past, 5-FU has been administered broadly to patients with HCC, with a large variation in dosages and schedules,[10–16] although as a single agent it has shown a low response rate and no influence on overall survival.[2,3] Mitoxantrone showed a similar tumor response and fewer myelotoxic and cardiotoxic effects than epirubicin or doxorubicin,[5–8] which is considered to be one of the most active chemotherapeutic agents against advanced HCC, with response rates ranging from 3% to 26%. Cisplatin has a broad spectrum of antineoplastic activity, and there have been several reports demonstrating its favorable effects against HCC.[7,8] Furthermore, among these three drugs, significant therapeutic synergism was observed against HCC[8,17,18] or other malignancies.[6] Therefore, we conducted a Phase II trial to evaluate the antitumor activity and toxicity of this combination systemic chemotherapy of 5-FU, mitoxantrone, and cisplatin in patients with metastatic HCC. The study subjects were patients with HCC with extrahepatic metastases because such patients, for whom standard treatments are not indicated, are the most appropriate candidates for clinical trials of systemic chemotherapy.[1–3] To our knowledge, this is the first clinical trial of systemic chemotherapy only for patients with metastatic HCC.

In the current study, 14 of 51 patients achieved a PR (i.e., a response rate of 27%), and adequate tumor shrinkage was induced to allow surgical resection in 2 patients. These results were comparable with, or better than, those of the other reported chemotherapeutic regimens (response rate range, 0–26%).[1–6,8–23] This regimen yielded relatively longer overall survival outcomes (median, 11.6 months) than the other reported

chemotherapeutic regimens (median overall survival range, 4–15.5 months),[1–6,8–23] although the outcome of the patients with metastatic HCC, who were enrolled in our study, was extremely poor.[1–3,24–26] Moreover, using this therapy, the serum AFP level was reduced > 50% in 6 of 28 patients (21%) who had shown a pretreatment level of ≥ 100 U/mL, and the serum PIVKA II level was reduced > 50% in 21 of 36 (58%) patients who had a pretreatment level of ≥ 100 mAU/mL. The response rates of tumor markers were also favorable.[9,12–15,19,20,23] Therefore, FMP therapy has significant antitumor activity against metastatic HCC.

Patients with HCC tend to experience more severe myelosuppression and hepatic toxicity than those with other malignant diseases. Most of the patients with HCC have cirrhosis, which is usually associated with compromised hepatic function, leukocytopenia, and thrombocytopenia.[1–3,24,26] In the current trial, the most common toxicities were neutropenia and leukocytopenia, but these toxicities were generally brief and reversible with the exception of one treatment-related death. Hepatic toxicity also was observed frequently, but it was difficult to differentiate between hepatic toxicity induced by FMP therapy and exacerbation of viral hepatitis because all patients presented with impaired baseline liver function. The serum transaminase levels of all patients who showed a ≥ Grade 3 elevation returned to baseline levels within 1 month, and these patients were able to continue chemotherapy without dose reduction. There was only one death attributable to chemotherapy toxicity and this regimen was generally tolerated in patients with advanced HCC.

HCC is considered primarily a chemoresistant disease. However, FMP therapy resulted in a relatively higher response rate and longer survival for patients with metastatic HCC. One of the reasons is that patients with poor hepatic reserve, poor performance status, refractory pleural effusion or ascites, or tumor thrombosis in the main portal trunk—reported to be unfavorable factors for tumor response to or prognosis after systemic chemotherapy24–27—were excluded from our study. Patt et al.[12] reported that patients who had lower levels of serum AFP before treatment (i.e., patients with a response rate of 31%) responded better to combination therapy with 5-FU and interferon than those with higher levels (i.e., patients with a response rate of 0%). Leung et al.[27] also reported that patients who have normal total bilirubin levels and noncirrhotic livers might have a ≤ 50% chance of response and prolonged survival after combination chemotherapy with cisplatin, doxorubicin, alpha-interferon, and 5-FU. There are some chemosensitive subgroups of patients with advanced HCC, and it is also important to identify the appropriate candidates for systemic chemotherapy as well as to explore novel therapeutic strategies.

FMP therapy has significant antitumor activity with acceptable toxicity in patients with metastatic HCC. However, such therapy has not been shown to confer any clinically meaningful survival advantage in comparison to other palliative therapies or best supportive care. Therefore, to support our findings, we emphasize the need for larger multicenter studies of FMP therapy including prospective randomized trials in patients with metastatic HCC.

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A Phase II Trial of Uracil–Tegafur (UFT) in Patients with Advanced Biliary Tract Carcinoma

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Background: Uracil–tegafur (UFT) has been reported to have broad antitumor activity in a variety of malignancies. However, its activity in biliary tract carcinoma has not been fully evaluated. The aim of this study was to evaluate the antitumor activity and toxicity of UFT in chemotherapy-naive patients with advanced biliary tract carcinoma.
Methods: Nineteen patients with advanced biliary tract carcinoma that was histologically confirmed as adenocarcinoma were enrolled in this phase II trial of UFT. A dose of 360 mg/m^2/day of UFT was administered orally if there was no evidence of tumor progression or there was unacceptable toxicity.
Results: Of the 19 patients evaluable for response, one patient (5%) achieved a partial response with a duration of 2.0 months. Six patients (32%) showed no change and the remaining 12 (63%) had progressive disease. The median survival, 6-month survival rate and 1-year survival rate for all patients were 8.8 months, 52.6 and 21.1%, respectively. The chemotherapy was well tolerated, because grades 3 or 4 toxicity were not observed.
Conclusion: UFT appears to have little activity as a single agent in treating patients with advanced biliary tract carcinoma. These findings do not support its use in practice, and further trials with this regimen in patients with biliary tract carcinoma are not recommended.

Key words: biliary tract carcinoma – chemotherapy – phase II study – uracil–tegafur

INTRODUCTION

Biliary tract carcinomas (BTCs), including carcinomas that arise from extrahepatic or intrahepatic bile duct, gallbladder or papilla of vater, are relatively rare tumors with a dismal prognosis. Surgical resection is the first choice of treatment for BTC and usually provides the only chance for a cure. However, because of the absence of early symptoms, the majority of patients are diagnosed with advanced stages of disease. Moreover, even for those who undergo surgical resection, the risk of recurrence is extremely high (1–3). To improve the prognosis of patients with this disease, effective chemotherapy is essential. However, no chemotherapeutic drug has yet shown sufficient efficacy to be acknowledged as a standard therapy, although various agents have been evaluated in clinical trials (1–3).

Uracil–tegafur (UFT) is an orally administered drug that is a combination of uracil and tegafur in a 4:1 molar concentration ratio. Uracil prevents degradation of 5-fluorouracil (5-FU) by inhibiting dihydropyrimidine dehydrogenase (DPD), which leads to an increased level of 5-FU in plasma and tumor tissues (4–6). It appears that prolonged administration of UFT results in a similar or higher maximum concentration achieved (C_{max}) as well as area under the curve (AUC) compared with those achieved with continuous infusion of 5-FU (7). In phase II trials in Japan, the antitumor activity of UFT was demonstrated in a variety of solid tumors including colorectal cancer and breast cancer (8,9). With regard to UFT for BTC, an overall response rate of 25% in eight evaluable patients was reported in a Japanese phase II trial in the early 1980s (8). However, the number of patients in that study was very small, and the results may have been unreliable because the quality of clinical trials in the early 1980s was debatable. Since then, the activity of UFT in BTC has not been re-evaluated, although UFT is approved and widely used for BTC in Japan and other countries. Therefore, we conducted a phase II trial to evaluate the antitumor activity and toxicity of UFT in patients with advanced BTC.

PATIENTS AND METHODS

ELIGIBILITY

Patients eligible for study entry had histologically or cytologically confirmed advanced BTC. The eligibility criteria were:

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20–74 years of age; an Eastern Cooperative Oncology Group performance status of 0–2; bidimensionally measurable disease; an estimated life expectancy ≥8 weeks after study entry; no prior chemotherapy; adequate hematological function (hemoglobin ≥11 g/dl, leukocytes ≥4000/mm^3, neutrophils ≥2000/mm^3 and platelets ≥100 000/mm^3); adequate hepatic function (serum total bilirubin ≤2.0 mg/dl and serum aspartate aminotransferase/alanine aminotransferase ≤2.5 times the upper limit of normal); adequate renal function (serum creatinine level within normal limits); and written informed consent. All patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage before treatment.

The exclusion criteria were: active infection; severe heart disease; refractory pleural effusion or ascites; active gastroduodenal ulcer; severe mental disorder; active concomitant malignancy; pregnant and lactating females; females of childbearing age unless using effective contraception; and other serious medical conditions.

Pre-treatment evaluation included taking a complete history and a physical examination. The pretreatment laboratory procedures were complete differential blood count, biochemistry tests and tumor markers including serum carcinoembryonic antigen (CEA) and serum carbohydrate antigen 19-9 (CA19-9). All patients underwent electrocardiography, chest radiography and computed tomography (CT) scan within the 4 weeks before study entry.

Treatment Schedule

UFT was administered orally at a dose of 360 mg/m^2/day. The total daily dose of UFT was divided into three doses administered every 8 h. When doses could not be divided evenly, the highest dose was given in the morning and the lowest dose in the evening. The calculated UFT dose was rounded off to the nearest 100 mg.

When ≥grade 3 hematological toxicity or ≥grade 2 nonhematological toxicity was observed, treatment was delayed until the toxicity subsided to grade 1 or less. If the daily dose of UFT was considered to be intolerable, the dose was reduced by 100 mg/day (one capsule/day). UFT was administered until the appearance of disease progression or unacceptable toxicity. Patients who were refractory to this regimen were allowed to receive any other anticancer treatments at their physician's discretion.

Response and Toxicity Evaluation

We used the Japan Society for Cancer Therapy criteria, which are fundamentally similar to the World Health Organization (WHO) criteria, for evaluating the tumor responses and the adverse effects. The objective tumor response was assessed by CT every 4 weeks after the beginning of UFT therapy. During this treatment, a complete differential blood count, serum chemistry profile and urinalysis were undertaken at least biweekly. Serum CEA and CA19-9 levels were measured every 4 weeks. Progression-free survival was defined as the time from the date of initial treatment to first documentation of progression or death. Overall survival was measured from the date of initial treatment to the date of death or the date of last follow-up.

Statistical Design

Analysis was to be performed when 19 patients were enrolled. In this study, the threshold response rate was defined as 5% and the expected response rate was set as 25%. If the lower limit of the 90% confidence interval (CI) exceeded the 5% threshold (objective response in four or more of the 19 patients), UFT was judged to be effective. If the upper limit of the 90% CI did not exceed the expected rate of 25% (zero or one objective response in the 19 patients), UFT was judged to be ineffective. If response was confirmed in two or three of the 19 patients, the decision whether or not to proceed to the next study was taken on the basis of the safety and survival data from the present study. In BTC, no chemotherapeutic drug has yet shown sufficient efficacy to be acknowledged as a standard therapy. Considering that this treatment also may be ineffective, the sample size in this study had to be set as a minimally required number of patients. Therefore, 90% was adopted as the CI, because the treatment could have been judged as ineffective due to the small sample size. This phase II trial was approved by the Institutional Review Board of the National Cancer Center.

RESULTS

Patients and Treatments

Nineteen patients were enrolled in this study at the two hospitals of the National Cancer Center between July 2002 and February 2004. The characteristics of the patients are listed in Table 1. A total of 33 courses were given, with an average of 1.7 courses (range 1–5) per patient. All patients discontinued this treatment because of disease progression. After abandoning UFT treatment, two patients received second-line chemotherapy with epirubicin, 5-FU and cisplatin (11); both patients showed stable disease with durations of 4.0 and 2.5 months, respectively. The remaining 17 patients received only best supportive care after the treatment.

Response

All 19 patients were evaluable for response. No patient achieved a complete response. One patient with gallbladder carcinoma achieved a partial response with a duration of 2.0 months, giving an overall response rate of 5% (95% CI 0–26). Six patients (32%) showed no change and the remaining 12 (63%) had progressive disease. During treatment, the serum CEA level was reduced by >50% of the pre-treatment level in only one patient, who achieved a partial response, and there was no patient whose serum CA19-9 level decreased from the pre-treatment level.

Table 1. Patient characteristics

Characteristic	No. of patients (%)
Age, years	
Median (range)	65 (50–74)
Gender	
Male	10 (53)
Female	9 (47)
ECOG performance status	
0	14 (74)
1	5 (26)
Prior surgery	
Positive	10 (53)
Primary site	
Gallbladder	8 (42)
Extrahepatic bile duct	2 (11)
Intrahepatic bile duct	8 (42)
Papilla of vater	1 (5)
Organs affected by metastases	
Liver	13 (68)
Lymph node	7 (37)
Lung	5 (26)
CEA (ng/ml)	
Median (range)	6.8 (2.9–133.5)
CA19-9 (U/ml)	
Median (range)	207 (4–56 000)

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 2. Toxicity

	Grade			
	1	2	3	4
Hematological toxicity				
Leukocytes	4 (21)	0 (0)	0 (0)	0 (0)
Neutrophils	2 (11)	1 (5)	0 (0)	0 (0)
Hemoglobin	1 (5)	1 (5)	0 (0)	0 (0)
Platelets	0 (0)	0 (0)	0 (0)	0 (0)
Non-hematological toxicity				
Nausea/vomiting	8 (42)	0 (0)	0 (0)	0 (0)
Stomatitis	2 (11)	0 (0)	0 (0)	0 (0)
Diarrhea	6 (32)	0 (0)	0 (0)	0 (0)
Fatigue	4 (21)	0 (0)	0 (0)	0 (0)
Alopecia	0 (0)	0 (0)	0 (0)	0 (0)
Skin rash	0 (0)	0 (0)	0 (0)	0 (0)
Hand–foot syndrome	0 (0)	0 (0)	0 (0)	0 (0)
Total bilirubin	–	6 (32)	0 (0)	0 (0)
Aspartate aminotransferase	8 (42)	1 (5)	0 (0)	0 (0)
Alanine aminotransferase	2 (11)	1 (5)	0 (0)	0 (0)
Alkaline phosphatase	4 (21)	0 (0)	0 (0)	0 (0)
Creatinine	2 (11)	0 (0)	0 (0)	0 (0)

Values in parentheses are percentages.

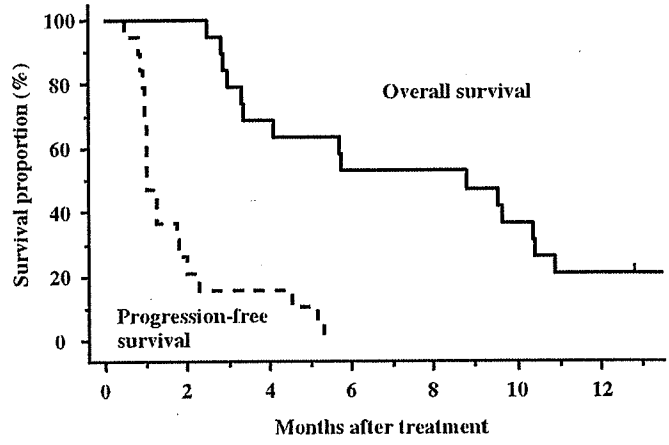

Figure 1. Overall survival and progression-free survival curves of 19 patients who received UFT therapy for advanced biliary tract carcinoma. Tick marks indicate censored cases.

TOXICITY

The toxicities observed in the 19 enrolled patients are listed in Table 2. The toxicity represents the maximum grade per patient for the entire course of therapy. Therapy with UFT was well tolerated, and all adverse events were manageable. Six patients (32%) showed grade 2 elevation of total bilirubin. However, the elevation in total bilirubin, which ranged from 1.1 to 2.0 times the upper limit of normal, was defined as grade 2 in the Japan Society for Cancer Therapy criteria, which is equivalent to grade 1 in the WHO criteria. No grade 3 or greater toxicities were observed in this study.

SURVIVAL

All enrolled patients were included in the survival assessment. At the time of the analysis, 18 patients had died because of tumor progression. The median survival, 6-month survival rate, 1-year survival rate and median progression-free survival for all patients were 8.8 months, 52.6%, 21.1% and 1.0 months, respectively (Fig. 1). The median survivals in patients with intrahepatic bile duct carcinoma and in those with other tumors, including carcinoma of the gallbladder, extrahepatic bile duct and papilla of vater, were 9.5 and 5.7 months, respectively.

DISCUSSION

The outcome of chemotherapy for BTC has not improved significantly in the last two decades, and the prognosis for patients with this disease still remains dismal. Because of

the rarity of this cancer, there have been few well-designed chemotherapeutic trials conducted with a sufficient number of patients. The most commonly used single agent has been 5-FU, with response rates of ≤10% and median survival times of ≤6 months (1–3). Mitomycin C, which was considered by some investigators to be one of the active agents for the treatment of this disease, resulted in an objective response rate of 10% in an EORTC study (12). Recently, gemcitabine has shown promising antitumor activity for BTC in several studies, with reported response rates of 8–60% and median durations of survival ranging from 6.5 to 11.5 months, but it has not yet been accepted as a standard therapy for BTC (13). Moreover, combination chemotherapy has also proven equally disappointing because it rarely results in any meaningful clinical improvement. Thus, various agents have been evaluated in clinical trials, but no chemotherapeutic drug has yet shown sufficient efficacy to be acknowledged as a standard therapy (1–3).

In Japan, only three anticancer agents, UFT, adriamycin and cytarabine, have been approved for BTC by the Ministry of Health, Labor and Welfare of Japan. UFT (tegafur combined with uracil in a molar ratio of 1:4) represents a second-generation oral 5-FU prodrug that is converted to 5-FU in tissue (4–6). Compared with 5-FU, UFT has been reported to be less toxic and to have a higher therapeutic index in a variety of solid tumors (8–9). In patients with BTC, a Japanese phase II study in the early 1980s demonstrated that UFT at a daily dose of 300–600 mg shows a relatively high response rate (two out of eight, 25%) (8). However, since then, the activity of UFT in BTC has not been re-evaluated. A re-appraisal of UFT for advanced BTC is essential, because the number of patients in the previous study was very small and the evaluation of tumor response may have been unreliable because in the early 1980s imaging modalities had not been developed sufficiently. To elucidate the true efficacy of UFT, therefore, we conducted a phase II trial of UFT in patients with advanced BTC.

In the current study, only one of 19 patients obtained a partial response (response rate, 5%) with a duration of 2.0 months. Moreover, a rate of progressive disease of 63% and a median progression-free survival of only 1 month were particularly disappointing. The results of this study indicate that UFT has negligible activity in BTC and, even though it was well tolerated, cannot be recommended as routine treatment for advanced BTC. In this study, there was a large difference between overall survival (median: 8.8 months) and progression-free survival (median: 1.1 months). The difference was assumed to be due to the natural history of this disease, because only two patients received second-line chemotherapy and the remaining 17 patients received only best supportive care after the treatment. In studies by Mani et al. (14) and Chen et al. (15), combination therapy with UFT and leucovorin resulted in 0% response rates and median survivals of 7.0 and 5.2 months, respectively. These results are very similar to ours, and this regimen was also considered ineffective. However, the novel oral fluoropyrimidine derivatives S-1 (16) and capecitabine (17) have generated particular interest for the treatment of advanced BTC, since the response rates with these agents are reported to be higher than that with UFT. Further trials of these agents are currently being conducted in patients with advanced BTC.

In conclusion, UFT appears to show little activity as a single agent in treating patients with advanced BTC, although oral UFT therapy is convenient and well tolerated. These findings do not support the use of this regimen in clinical practice, and further trials in patients with BTC are not recommended. Therefore, we will continue to investigate other agents and regimens in an effort to increase response, survival and quality of life for patients with this disease.

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Chemoradiotherapy for Locally Advanced Pancreatic Carcinoma in Elderly Patients

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Key Words
Chemoradiotherapy · Pancreatic carcinoma · Elderly

Abstract
Objectives: Chemoradiotherapy, which is one of the standard treatments for locally advanced pancreatic carcinoma, is considered a high-risk procedure in elderly patients. This study investigated the outcome and tolerability of this treatment in elderly patients. ***Methods:*** We reviewed our database from November 1993 to March 2003 and retrospectively examined the clinical data of patients with histologically confirmed exocrine pancreatic carcinomas that were nonresectable but confined to the pancreatic region, who were treated with protracted 5-fluorouracil infusion (200 mg/m^2/day) and concurrent radiotherapy (50.4 Gy in 28 fractions over 5.5 weeks). We evaluated the outcome of patients ≥70 years and those <70 years. ***Results:*** There were 19 patients ≥70 and 39 patients <70. On pretreatment evaluation, the elderly patients showed lower serum albumin levels, lower transaminase levels, better ECOG performance status, more frequent body weight loss and less frequent abdominal and/or back pain with the administration of morphine than the younger patients. There were no significant differences in the frequency of severe toxicity. Neither the response rate nor the incidence of treatment discontinuation differed significantly between the two groups. The median survival time was longer in the elderly patients than in the younger patients (11.3 vs. 9.5 months, p = 0.04). ***Conclusions:*** With careful patient selection, chemoradiotherapy can be one of the treatment options for locally advanced pancreatic carcinoma in elderly patients.

Introduction

The prognosis of patients with pancreatic carcinoma is extremely poor because of difficulty in the early detection of this disease and the ineffectiveness of nonsurgical treatments. For patients with locally nonresectable disease, the results of previous randomized trials indicated that concurrent external beam radiation therapy (EBRT) and 5-fluorouracil (5-FU) therapy resulted in significantly better survival compared with EBRT alone [1, 2] or chemotherapy alone [3]. However, this combination treatment sometimes induces intolerable toxic effects, and approximately 10–20% of patients cannot complete the scheduled course of treatment [4, 5]. Consequently, this treatment is considered to be frequently contraindicated in elderly patients, who are thought to be less likely to tolerate its potential toxicity than younger patients.

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Furthermore, many physicians believe that pancreatic carcinoma is less treatable in the elderly because of the presence of comorbid illnesses. On the other hand, it was reported that elderly patients often tolerate aggressive chemotherapy or radiotherapy for other carcinomas as well as their younger counterparts [6–16].

Some studies have shown that for resectable pancreatic carcinoma, pancreatic resections can be performed for the elderly with acceptable morbidity and mortality rates and possible long-term outcome [17–25]. However, in locally advanced pancreatic carcinoma treated with chemoradiotherapy, the tolerability, efficacy of treatment and long-term outcome have not been discussed extensively.

The current retrospective analysis examines the outcome and tolerability of elderly patients (i.e. those aged ≥70 years) within our database. The main purposes of this examination were to determine if the outcome for elderly patients was different from that for younger patients and to characterize the toxicity experienced by the elderly patients.

Methods

We reviewed the database of the Hepatobiliary and Pancreatic Oncology Division of the National Cancer Center Hospital from November 1993 to March 2003. In this retrospective analysis, we examined the clinical data of all patients who met the following requirements: (1) histological diagnosis of exocrine pancreatic carcinoma, (2) nonresectable disease confined to the pancreatic region, (3) treatment with protracted 5-FU infusion and concurrent radiotherapy, and (4) absence of prior treatment for pancreatic carcinoma. We divided the patients into two groups according to age, those ≥70 years and those <70 years. We evaluated the patient characteristics, toxicities, efficacies and survival in both groups.

Treatment was performed according to the treatment protocol of our division; radiotherapy was delivered via a microtron (MM22, Scanditronix, Upsala, Sweden) with 10- or 14-MV X-rays or a racetrack microtron (MM50, Scanditronix) with 25-MV X-rays. A total dose of 50.4 Gy was delivered in 28 fractions over 5.5 weeks. All patients had treatment planning computed tomography (CT) scans (X-vision, Toshiba, Tokyo, Japan), and FOCUS (Computerized Medical Systems, St. Louis, Mo., USA) was used as a radiotherapy treatment planning system. The clinical target volume included the primary tumor, nodal involvement detected by CT scan, and regional draining and para-aortic lymph nodes, which included the peripancreatic nodes, celiac and superior mesenteric axes. The planning target volume was defined as the clinical target volume plus a 10-mm margin. Four field techniques (anterior, posterior and opposed lateral fields) were used. The spinal cord dose was maintained below 45 Gy, ≥50% of the liver was limited to ≤30 Gy, and ≥50% of both kidneys was limited to ≤20 Gy. 5-FU was given from the first day of radiation and continued through the entire course of radiation at a dose of 200 mg/m^2/day through a central venous catheter. Patients were admitted to the hospital during chemoradiotherapy. Within 8 weeks after the completion of chemoradiotherapy, maintenance chemotherapy was delivered on an outpatient basis and continued until disease progression. For the maintenance chemotherapy, we used a weekly administration of 5-FU (500 mg/m^2, 30-min infusion) before the approval of gemcitabine for pancreatic carcinoma in Japan (April 2001), and thereafter, we used weekly administration of gemcitabine (1,000 mg/m^2, 30-min infusion) 3 times every 4 weeks.

During chemoradiotherapy, the toxicity of the treatment was scored weekly according to the World Health Organization criteria [26]. Both radiotherapy and chemotherapy were suspended when ≥grade 3 toxicities other than anorexia, fatigue, nausea/vomiting, constipation and hyperglycemia occurred and were resumed when recovery to grade 2 toxicity levels was achieved. If there was a total delay of 2 weeks due to toxicity for any reason, the combined treatment was discontinued. In this retrospective analysis, we obtained the information regarding adverse events about the subjective symptoms from the doctor's record in as much detail as possible. As a rule, follow-up CT was performed within 1 week after the completion of chemoradiotherapy and every 2 months thereafter to evaluate the objective tumor response with reference to the World Health Organization criteria.

Statistics

Frequencies in 2 × 2 and larger contingency tables of the patient characteristics, response rates and toxicities were compared with the χ^2 or Fisher's exact test. Distributions of continuous variables were compared with the Mann-Whitney test. Overall survival was measured from the first day of treatment, and the survival curves were calculated according to the Kaplan-Meier method. The log rank test was used to detect differences between the curves. All p values in this study were of the two-tailed type. Significance was defined as a p value of 0.05 or less. Statistical analyses were performed with Stat View version 5.0.

Results

One hundred and ninety-nine patients with locally advanced pancreatic carcinoma admitted to the Hepatobiliary and Pancreatic Oncology Division of the National Cancer Center Hospital from November 1993 to March 2003. Thirty-nine patients were ≥70 years and 160 were <70 years. Nineteen (49%) of the 39 patients ≥70 and 39 (24%) of the 160 of those <70 met the above-mentioned conditions. The remaining 141 patients were excluded from this analysis. One hundred and thirty-eight received other anticancer treatments including chemoradiotherapy using other regimens (130), systemic chemotherapy (7) and radiotherapy alone (1). Three patients underwent only the best supportive care. The patient characteristics are shown in table 1 and the pretreatment laboratory data are shown in table 2. The male-to-female ratio was 1.7:1 in the elderly patients and 1.4:1 in the younger patients.

Table 1. Patient characteristics

	≥70 years	<70 years	p
Patients	19	39	
Age			
Median	75	60	
Range	70–86	35–69	
Sex			0.78
Male	12 (63)	23 (59)	
Female	7 (37)	16 (41)	
ECOG PS			0.004
0	6 (32)	1 (3)	
1	11 (58)	36 (92)	
2	2 (11)	2 (5)	
Diabetes mellitus	9 (47)	10 (26)	0.14
Abdominal and/or back pain[a]	3 (16)	19 (49)	0.02
Biliary drainage	4 (21)	8 (21)	>0.99
Regional lymph node	11 (58)	22 (56)	>0.99
Body weight loss[b]	14 (74)	24 (62)	0.20
Tumor location			0.42
Uncus	1 (5)	5 (13)	
Head	12 (63)	25 (64)	
Body	5 (26)	9 (23)	
Tail	1 (5)	0 (0)	
Treatment start			>0.99
Before April 2001[c]	10 (53)	21 (54)	
After April 2001[c]	9 (47)	18 (46)	

Figures in parentheses are percentages. ECOG = Eastern Cooperative Oncology Group.

[a] Abdominal and/or back pain: with consumption of morphine.

[b] Body weight loss: more than 7% of previous body weight within 6 months.

[c] April 2001: approval of gemcitabine.

Table 2. Pretreatment laboratory data

	≥70 years	<70 years	p
Albumin, g/dl	3.6 (3.0–4.3)	3.8 (3.1–4.5)	0.002
AST, IU/l	19 (11–66)	23 (10–274)	0.04
ALT, IU/l	17 (9–136)	32 (6–332)	0.01
Total bilirubin, mg/dl	0.7 (0.3–1.3)	0.6 (0.2–3.7)	0.20
CA19-9, U/ml	769.5 (3–27,000)	624.0 (4–6,310)	0.06
CEA, ng/ml	6.9 (2.1–76.4)	4.9 (0.7–1,620)	0.11

AST = Aspartate aminotransferase; ALT = alanine aminotransferase; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen.

Table 3. Response to chemoradiotherapy

	≥70 years	<70 years	p
Complete response	0 (0)	0 (0)	
Partial response	2 (11)	2 (5)	
No change	14 (74)	28 (72)	
Progressive disease	3 (16)	7 (18)	
Not evaluable	0 (0)	2 (5)	0.60

Figures in parentheses are percentages.

In the elderly patients, there were 6 patients (32%) who had an ECOG performance status (PS) of 0, but there was only 1 such patient (3%) among the younger patients ($p = 0.004$). The incidence of patients who had abdominal or back pain with consumption of morphine was smaller in the elderly patients ($p = 0.02$). There was no significant difference between the younger and elderly patients with regard to the period prior to treatment initiation (before or after the gemcitabine approval) ($p > 0.99$). The serum albumin level and transaminase levels were lower in the elderly patients. The other patient characteristics of those ≥70 years were generally similar to those of the younger patients.

The results of the treatment outcome are shown in table 3. Even though this study was conducted retrospectively, the antitumor response in CT was obtained in all but 2 younger patients who were transferred to another hospital before the completion of treatment. The laboratory data were also maintained for all patients, whose blood examinations were performed at least weekly. Four subjects among the elderly patients (21%) suspended the chemoradiotherapy during the schedule, as did 11 (28%) among the younger patients. One elderly patient (5%) discontinued chemoradiotherapy, as did 5 (13%) of the younger patients. Chemoradiotherapy was discontinued because of patient request due to unacceptable toxicities such as fatigue (1 younger patient), nausea/vomiting (3 younger patients and 1 elderly patient) and patient refusal (1 younger patient). A partial response was obtained in 2 (11%) elderly and 2 (5%) younger patients. Fourteen (74%) elderly patients and 28 (72%) younger patients showed no change. The survival curves are shown in figure 1. The median survival time was longer for the elderly patients than for younger patients (11.3 months in the elderly patients, 9.5 months in the younger patients, $p = 0.04$). The longest survivor in both groups was a 71-year-old male who survived 60.1 months (5.0 years) after the initiation of treatment.

Table 4. Toxicity in patients receiving chemoradiotherapy

	Grades 1–4		p	Grades 3 and 4		p
	≥70 years	<70 years		≥70 years	<70 years	
Leukocytes	9 (47)	20 (51)	>0.99	1 (5)	2 (5)	>0.99
Hemoglobin	8 (42)	16 (41)	>0.99	0 (0)	0 (0)	–
Neutrophils	3 (16)	12 (31)	0.37	0 (0)	0 (0)	–
Platelets	4 (21)	4 (10)	0.48	0 (0)	0 (0)	–
Albumin	10 (53)	16 (41)	0.58	0 (0)	0 (0)	–
AST	4 (21)	8 (21)	>0.99	0 (0)	2 (5)	0.81
ALT	3 (16)	15 (38)	0.15	0 (0)	3 (8)	0.54
Total bilirubin	2 (11)	3 (8)	>0.99	0 (0)	1 (3)	>0.99
Creatinine	2 (11)	0 (0)	0.2	0 (0)	0 (0)	–
Nausea	11 (58)	34 (87)	0.03	2 (11)	13 (33)	0.12
Vomiting	4 (21)	19 (49)	0.07	0 (0)	1 (3)	>0.99
Anorexia	16 (84)	35 (90)	0.9	6 (32)	22 (56)	0.13
Stomatitis	3 (16)	2 (5)	0.85	1 (5)	0 (0)	0.71
Diarrhea	4 (21)	13 (33)	0.47	0 (0)	2 (5)	0.81
Fatigue	3 (16)	13 (33)	0.28	0 (0)	1 (3)	>0.99

Figures in parentheses are percentages. AST = Aspartate aminotransferase; ALT = alanine aminotransferase.

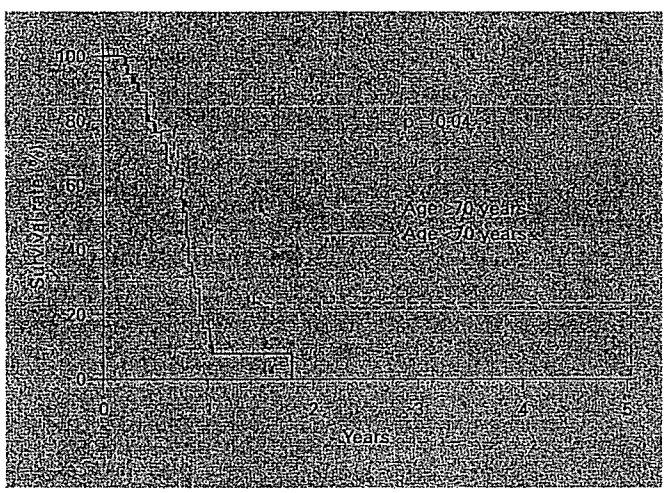

Fig. 1. Overall survival curves for patients ≥ 70 years (n = 19) and those for patients <70 years (n = 38).

The percentages of overall toxicities (grades 1–4) and severe toxicities (grades 3 and 4) are listed in table 4. Although the incidence of nausea (grades 1–4) was significantly higher in the younger patients, there were no significant differences in the incidence of other overall toxicities or all severe toxicities. The toxicities of both groups were generally mild and reversible. One younger patient died from a fungal infection of the lung due to pneumothorax which occurred as a complication of the insertion of a central venous catheter. There was no conspicuous late toxicity in either group.

Discussion

Based on previous randomized trials [1–3], concurrent EBRT and 5-FU result in significantly better survival compared with EBRT alone or chemotherapy alone and are generally accepted as the standard treatment for locally advanced pancreatic carcinoma. However, this treatment restrains patients for more than 1.5 months during treatment. Furthermore, the life expectancy for the majority of these patients is still short, with a median survival of approximately 10–11 months. The poor prognosis and long duration of treatment makes us hesitant to indicate chemoradiotherapy for patients with locally advanced pancreatic carcinoma, especially for patients at high risk for complications. Elderly patients have been generally considered a high-risk population for chemoradiotherapy due to a number of physiological and pharmacological reasons. For example, diminished bone marrow cellularity can potentially result in decreased tolerance to myelosuppressive therapies. In addition, a decrease in hepatic and renal function may reduce the efficiency of drug metabolism and excretion, resulting in greater toxic potential.

However, in this study, no differences were found in the response rate, incidence of treatment discontinuation and toxicity profile, except for nausea, between the two groups. The median survival time was significantly longer in the elderly patients than in the younger patients. The most important reason for the favorable results of the elderly patients may be the careful selection of patients. Ikeda et al. [27] reported that a good PS was one of the independent favorable prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. In our study, 32% of the patients ≥70 had an ECOG PS of 0, as opposed to 3% of those <70. Since this was a retrospective analysis, indication according to a physician's decision might have been different for younger and for elderly patients, only allowing the elderly patients in very good condition to receive chemoradiotherapy. As a result, this may be a comparison of elderly patients with a very good PS and younger patients with a less good or average PS.

An imbalance in the incidence of patients with abdominal pain between the two groups might also have affected the treatment outcome in our study. According to the report of Kelsen et al. [28], unresectable pancreatic carcinoma patients with abdominal pain had a median survival of 4.7 months, whereas the median survival among patients without such pain was 8.3 months.

In this study, there was no significant difference between the younger patients and the elderly patients with regard to the ratio of the patients who received maintenance chemotherapy using gemcitabine. Although it is possible that maintenance therapy had some effect on survival, the survival time did not differ significantly between the gemcitabine maintenance chemotherapy group and the 5-FU maintenance chemotherapy group in this study (data not shown).

The mild toxicity of this treatment may be another favorable factor for elderly patients [4]. This study showed that severe toxicities except anorexia were observed infrequently in both groups and that discontinuation of the treatment was required in only 1 elderly patient. Protracted 5-FU infusion with concurrent radiotherapy, which is considered a less toxic treatment than radiotherapy and bolus 5-FU [29, 30], is feasible even in elderly patients.

Krzyzanowska et al. [31] reported an attractive retrospective cohort study in 1,696 patients diagnosed with locally advanced pancreatic carcinoma. According to the report, older age was associated with a lower likelihood of receiving carcinoma-directed therapy, much less of a combined therapy such as chemoradiotherapy. However, Cox proportional hazard models showed that carcinoma-directed therapy, including chemoradiotherapy, has the potential to prolong the survival of elderly patients with locally advanced pancreatic carcinoma. These findings, which suggest that chemoradiotherapy can be an optimal treatment option for locally advanced pancreatic carcinoma in elderly patients, are supported by the results of our study.

Since this study was conducted retrospectively, the results do nothing more than suggest possibilities of the efficacy of the 5-FU-based chemoradiotherapy for selected elderly patients with locally advanced pancreatic carcinoma. To identify the benefit of the treatment in elderly patients, we must design a large prospective study. In summary, this study demonstrates that chemoradiotherapy for locally advanced pancreatic carcinoma is well tolerated and does not lead to an increase in treatment interruption or discontinuation in elderly patients. We conclude that, with careful patient selection, chemoradiotherapy can be considered an appropriate treatment for elderly patients.

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