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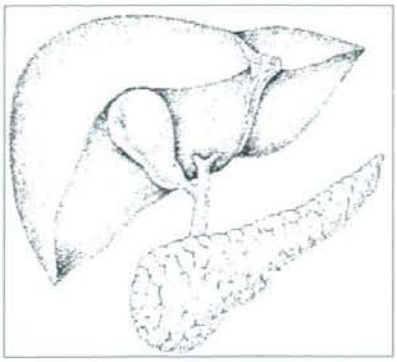

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Adjuvant treatments for resectable pancreatic cancer

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Abstract
Pancreatic cancer remains one of the most challenging malignancies to treat successfully. The majority of patients present with unresectable advanced-stage cancer, and only 20% of patients can undergo resection. Even if surgical resection is performed, the recurrence rate is high and the survival rate after surgery is poor. Therefore, effective adjuvant therapy is needed to improve the prognosis of patients with pancreatic cancer. Until now, no universally accepted standard adjuvant therapy for this disease has been available: chemoradiotherapy followed by chemotherapy is considered the optimal therapy in the United States, while chemotherapy alone is the current standard in Europe. However, recent randomized controlled trials (RTOG [Radiation Therapy Oncology Group] 9704; CONKO [Charité Onkologie]-001; and a Japanese study) have suggested a benefit of adjuvant chemotherapy with gemcitabine for patients with resectable pancreatic cancer. This article will review the clinical trials of adjuvant therapy for this disease, including the results of recent trials.

Key words Pancreatic cancer · Adjuvant therapy · Chemoradiotherapy · Chemotherapy

Introduction

Surgical resection offers the only opportunity for cure in patients with pancreatic cancer; therefore, detection at an early stage, especially International Union Against Cancer (UICC) stage I, is essential to increase long-term survival. However, no valid method of screening has been established for this disease, and only 20% of all pancreatic cancers are detected at the resectable stage. In addition, because the recurrence rate after surgery is high, the 5-year survival rate in patients with resectable pancreatic cancer is 20% or less. Because surgical resection alone has limitations, the development of nonsurgical treatment as adjuvant therapy is important. Recently, various attempts at adjuvant therapy have been reported for this disease. This review focuses on the outcomes of clinical trials, including randomized controlled trials (RCTs), of adjuvant therapy for resectable pancreatic cancer.

Controversies associated with adjuvant therapy for pancreatic cancer

For breast cancer and colorectal cancer, the survival benefits of adjuvant therapy in resectable cases have been shown in large-scale RCTs, and a standard adjuvant therapy has been established on a global scale. In regard to pancreatic cancer, the survival benefits of chemotherapy using gemcitabine (GEM) for unresectable advanced cases have been evaluated internationally. However, as far as adjuvant therapy for resectable pancreatic cancer is concerned, no globally accepted standard therapy has yet been established. Major factors underlying this situation are: (1) difficulty in conducting large-scale RCTs because the number of resectable pancreatic cancer cases is not large enough; and (2) lack of consensus about the significance of adjuvant chemoradiotherapy between United States and European physicians. According to the results of clinical studies including RCTs carried out in the United States and Europe, most United States physicians now support the validity of adjuvant chemoradiotherapy, while most in Europe have a negative view of adjuvant chemoradiotherapy and a positive view of adjuvant chemotherapy. It is therefore difficult to establish an adjuvant therapy which can serve as a global standard, and it is desirable that global cooperative studies be carried out to reach a consensus regarding the validity of adjuvant therapy.

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Adjuvant chemoradiotherapy

Table 1 summarizes the results of RCTs reported to date on adjuvant chemoradiotherapy for resectable pancreatic cancer. The GITSG (Gastrointestinal Tumor Study Group)[1] and RTOG (Radiation Therapy Oncology Group) 9704[2] trials were carried out in the United States, and the EORTC (European Organization for Research and Treatment of Cancer)[3] and ESPAC (European Study Group For Pancreatic Cancer)-1[4] trials were carried out in Europe.

Although GITSG is an RCT that was carried out more than 20 years ago,[1] the results of this study still have major impacts even at present. In this RCT, the adjuvant chemoradiotherapy group was compared with an observation group, yielding a significantly longer survival period in the former, with the median survival time (MST) being 20 months vs 11 months ($P = 0.035$). The regimen evaluated in GITSG was a combination of split-course radiotherapy (20 Gy × 2) and bolus 5-fluorouracil (5-FU) injection, followed by maintenance chemotherapy using bolus 5-FU injection. This RCT has been criticized for the very small scale of the study (only 43 subjects were analyzed because of difficulties in case enrollment) and the poor results in the observation group despite curative resection being carried out in these patients. However, because no RCT results that invalidate the results of the GITSG have been reported from the United States, many clinicians in the United States still consider chemoradiotherapy as a standard adjuvant therapy for resectable pancreatic cancer.

In Europe, an RCT was carried out by EORTC as a follow-up to the GITSG.[3] The regimen evaluated in the EORTC trial resembled that employed in GITSG, except that 5-FU was administered by continuous intravenous infusions during irradiation and no maintenance chemotherapy was used. The EORTC trial involved 114 subjects (larger than the number of GITSG subjects) and demonstrated a tendency for slightly better outcomes in the chemoradiotherapy group as compared to the observation group, although the difference was not statistically significant (MST, 17.1 months vs 12.6 months; $P = 0.099$). Following the report of the EORTC trial results, European clinicians began to question the efficacy of postoperative chemoradiotherapy for resectable pancreatic cancer, but some commented that, in view of the slightly better outcomes in the chemoradiotherapy group, a significant difference in outcome would have been obtained if a larger number of subjects had been studied. In response to the criticism that the scales of the studies were too small to draw any valid conclusions from the GITSG and EORTC trials, a larger-scale RCT was planned by ESPAC in the 1990s (ESPAC-1).[4] In this RCT, not only the significance of chemoradiotherapy but also that of chemotherapy was assessed using the 2 × 2 factorial design. ESPAC-1 adopted the GITSG regimen for chemoradiotherapy and a combined 5-FU + leucovorin (LV) regimen for chemotherapy. The final analysis of the data from 289 subjects revealed a survival-prolonging effect of chemotherapy, but chemoradiotherapy exerted no significant efficacy as compared to the group who did not receive chemoradiotherapy, with the outcome being less favorable in the chemoradiotherapy group than in the no-chemoradiotherapy group (MST, 15.9 months vs 17.9 months; $P = 0.053$). Although some problems have been raised regarding this study (e.g., quality control for radiotherapy, low compliance with the instructions on the assigned therapy, and problems with the analytical method), many European clinicians now view postoperative chemoradiotherapy negatively.

In the United States, there was a long break in reports on RCTs of adjuvant therapy for resectable pancreatic cancer. Recently, the RTOG presented the results of a

Table 1. Randomized controlled trials of adjuvant chemoradiotherapy for resectable pancreatic cancer

Author	Year of publication	Treatment	Number of patients	MST (months)	2-Year survival rate	*P* value (log-rank test)
Kalser and Ellenberg[1] (GITSG)	1985	5-FURT → 5-FU	21	20	42%	0.035
		Observation	22	11	15%	
Klinkenbijl et al.[3] (EORTC)	1999	5-FURT	60	17.1	37%	0.099
		Observation	54	12.6	23%	
Neoptolemos et al.[4] (ESPAC-1)	2004	5-FURT	145	15.9	29%	0.053
		No 5-FURT	144	17.9	41%	
Regine et al.[2] (RTOG 9704)	2006	All patients				
		GEM → 5-FURT → GEM	221	18.8	NA	0.15
		5-FU → 5-FURT → 5-FU	221	16.9	NA	
		Pancreas head only				
		GEM → 5-FURT → GEM	187	20.6	NA	0.033
		5-FU → 5-FURT → 5-FU	194	16.9	NA	

5-FURT, chemoradiotherapy using 5-fluorouracil; 5-FU, 5-fluorouracil; GEM, gemcitabine; MST, median survival time; NA, not available

large-scale RCT involving the analysis of the data from 442 subjects.[2] This RCT was designed to identify an optimal chemotherapy to be added to chemoradiotherapy, rather than to evaluate the validity of chemoradiotherapy. Chemoradiotherapy using 5-FU was administered to both groups, and 5-FU was compared with GEM as the agent used for chemotherapy to be added to chemoradiotherapy. When the data from the entire population were analyzed, no significant difference in the survival period was noted between the 5-FU group and the GEM group, but the GEM group had significantly better outcomes when the analysis was confined to cases of pancreatic head cancer (MST, 20.6 months vs 16.9 months; $P = 0.033$). There is an open question as to the meaning of the significant difference demonstrated by the analysis of pancreatic head cancer alone. At present, however, chemoradiotherapy using 5-FU is often combined with chemotherapy using GEM in the United States.

As a new attempt at chemoradiotherapy, combinations of GEM and radiotherapy have been actively studied since the latter half of the 1990s. Because this combined therapy was shown to induce relatively intense adverse reactions, modifications of the regimen have been called for, e.g., reducing the GEM dose level and/or radiation dose or narrowing the irradiated field. Blackstock et al.[5] conducted a phase II study, using a regimen combining twice weekly GEM treatment (40 mg/m^2) with 50.4 Gy radiotherapy, and reported an MST of 18.3 months. At present, a large-scale RCT by EORTC is underway, comparing GEM followed by chemoradiotherapy using GEM vs GEM alone (EORTC 40013). As another noteworthy chemotherapeutic approach, we can cite a regimen involving the combined use of three drugs (5-FU, cisplatin, and interferon-alpha) reported by the Mason Medical Center. The investigators at this facility applied this therapy in 43 patients who had undergone surgical resection, and reported a very favorable outcome (5-year survival rate of 55%).[6] At present, a multicenter phase II study (ACOSOG [American College of Surgeons Oncology Group]-Z05031) is underway in the United States to assess the reproducibility of this study. In Germany, an RCT (CapRI [adjuvant ChemoRadioImmunotherapy of pancreatic carcinoma] trial) is now underway, comparing chemoradiotherapy using a combination of these three drugs with the chemotherapeutic regimen used in the ESPAC-1 trial (5-FU + LV).[7]

In recent years, active efforts have been made to develop adjuvant therapy combining radiotherapy with new treatment modalities such as molecular-targeted drugs and vaccine therapy. To date, the efficacies of these new therapies remain to be clarified.

Adjuvant chemotherapy

Table 2 summarizes the results of RCTs reported to date concerning adjuvant chemotherapy for resectable pancreatic cancer. As stated above, adjuvant chemoradiotherapy began to be used as a standard therapy in the 1980s in the United States. For this reason, evaluation of adjuvant chemotherapy is difficult in the United States. Evaluation of adjuvant chemotherapy has thus been carried out primarily in Europe and Japan.

5-FU had been used as a major drug for adjuvant chemotherapy since before GEM began to be used for pancreatic cancer in the latter half of the 1990s. Several combined therapy regimens involving 5-FU had been attempted during that period. The earliest attempt was the RCT reported in 1993 by Bakkevold et al.[8] from Norway. In that study, postoperative AMF therapy

Table 2. Randomized controlled trials of adjuvant chemotherapy for resectable pancreatic cancer

Author	Year of publication	Treatment	Number of patients	MST (months)	2-Year survival rate	*P* value (log-rank test)
Bakkevold et al.[8] (Norway)	1993	ADR + MMC + 5-FU	30[a]	23	43%	0.10
		Observation	31[a]	11	32%	
Takada et al.[9] (Japan)	2002	5-FU + MMC	81	NA	NA	NS
		Observation	77	NA	NA	
Neoptolemos et al.[4] (ESPAC-1)	2004	5-FU + LV	147	20.1	40%	0.009
		No 5-FU + LV	142	15.5	30%	
Kosuge et al.[10] (Japan)	2006	5-FU + cisplatin	45	12.5	NA	0.94
		Observation	44	15.8	NA	
Oettle et al.[12] (CONKO-001)	2007	GEM	179	22.1	47.5%	0.06
		Observation	175	20.2	42%	
Kosuge et al.[13] (Japan)	2007	GEM	58	22.3	48.3%	0.29
		Observation	60	18.4	39.8%	

ADR, adriamycin; MMC, mitomycin C; 5-FU, 5-fluorouracil; LV, leucovorin; GEM, gemcitabine; MST, median survival time; NA, not available; NS, not significant

[a] Including ampulla of Vater cancer

(adriamycin + mitomycin C + 5-FU) was compared with observation, involving 61 patients with surgically resected pancreatic cancer, including ampulla of Vater cancer. The authors reported that the MST was longer in the chemotherapy group (23 months) than in the observation group (11 months), although analysis of the overall survival period revealed no significant intergroup difference.[8] In Japan, Takada et al.[9] compared combined 5-FU + mitomycin C therapy with observation, and Kosuge et al.[10] compared combined 5-FU + cisplatin therapy with observation, but neither of these studies revealed a significant intergroup difference in survival periods.

In contrast to these studies, the ESPAC-1 trial[4] revealed the usefulness of adjuvant chemotherapy involving 5-FU. When the adjuvant chemotherapy (5-FU + LV) was analyzed using a 2×2 factorial design in that study, the survival time was significantly longer in the adjuvant chemotherapy group than in the group without adjuvant chemotherapy (MST, 20.1 months vs 15.5 months; $P = 0.009$).[4] A metaanalysis was conducted on the results of RCTs reported before ESPAC-1 (GITSG,[1] EORTC,[3] Bakkevold et al.,[8] Takada et al.,[9] ESPAC-1[4]).[11] The analysis revealed that chemotherapy involving 5-FU reduced the risk of death significantly (hazard ratio, 0.75; 95% confidence interval, 0.64–0.90; $P = 0.001$). The ESPAC-1[4] findings, which revealed the survival benefit of adjuvant chemotherapy in a large-scale RCT, now have major impacts, and there is a prevailing view in Europe that chemotherapy should be used as a standard adjuvant therapy for resectable pancreatic cancer.

Next to 5-FU, GEM has been actively studied in the adjuvant setting. German investigators, including Oettle et al.,[12] compared a GEM therapy group with an observation group after surgical resection of pancreatic cancer (CONKO [Charité Onkologie]-001). The results of their study were presented at an American Society of Clinical Oncology (ASCO) 2005 meeting. In the CONKO-001 study, GEM was administered for six courses by the routine dosing method. The data from 354 patients in total from the two groups were analyzed. The disease-free survival (DFS), which served as a primary endpoint of the study, was significantly longer in the GEM group than in the observation group (median DFS, 13.4 months vs 6.9 months; $P < 0.001$). In the analysis of overall survival, the survival period tended to be longer in the GEM group than in the observation group, although this difference was not statistically significant (MST, 22.1 months vs 20.2 months; $P = 0.06$).

An RCT of GEM vs observation has also been conducted in Japan, and the results were reported at an European Cancer Conference (ECCO) 14 meeting.[13] In that study, data from 118 subjects were analyzed, and the GEM group received three treatment courses (shorter than the period in the CONKO-001 study). The DFS was significantly longer in the GEM group than in the observation group (median DFS, 11.4 months vs 5.0 months; $P = 0.01$). In the analysis of overall survival, the GEM group tended to show more favorable results than the observation group, but the difference was not significant (MST, 22.3 months vs 18.4 months; $P = 0.29$). Most of the adverse reactions of GEM observed in that study were temporary, and severe adverse reactions were rare. The results of GEM therapy in Japan were quite akin to those of the CONKO-001 study. This high reproducibility suggests the effectiveness of adjuvant chemotherapy using GEM.

In Europe, a large-scale RCT (ESPAC-3) involving comparisons among three groups (observation, 5-FU + LV, and GEM) is now underway. In Japan, active efforts are currently being made to develop novel adjuvant chemotherapy using S-1, following the report of favorable outcomes of S-1 therapy for advanced pancreatic cancer.[14]

Conclusions

Although no adjuvant chemotherapy that serves as a global standard for pancreatic cancer has yet been established, RCTs of this type of therapy have been actively performed in recent years, yielding increasing evidence of the benefits of such therapy.

In Japan, GEM has increasingly been accepted as the treatment of choice for patients after the surgical resection of pancreatic cancer, based on the CONKO-001 trial[12] and the results of a Japanese RCT.[13] Because the prognosis of patients with pancreatic cancer is still poor, advances based on research into adjuvant therapy are desired. When considering the adoption of adjuvant therapies in clinical cases, it is essential to adequately inform individual patients of the fact that no universally accepted standard adjuvant therapy has yet been established for pancreatic cancer, in addition providing an explanation of adverse reactions. Then, if the patient agrees to undergo adjuvant therapy, the treatment should be carried out carefully, paying close attention to adverse reactions.

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ORIGINAL ARTICLE

A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer

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Abstract
Purpose Gemcitabine monotherapy or gemcitabine-containing combination chemotherapy is the standard first-line therapy for advanced pancreatic cancer. After disease progression, there is no standard regimen available. In a previous phase II trial, S-1 has been reported to show considerable efficacy, achieving a response rate of 37.5% in chemo-naïve patients with pancreatic cancer. This study evaluated the efficacy and toxicity of S-1 in patients with gemcitabine-refractory metastatic pancreatic cancer.
Methods Eligibility criteria were histologically proven pancreatic adenocarcinoma with confirmation of progressive disease while receiving gemcitabine-based first-line chemotherapy, 20–74 years of age, Karnofsky performance status of 80–100 points, with measurable metastatic lesions, adequate hematological, renal and liver functions, and written informed consent. S-1 was administered orally at 40 mg/m^2 twice daily for 28 days with a rest period of 14 days as one course. Administration was repeated until the appearance of disease progression or unacceptable toxicity. The primary endpoint of this study was an objective response, and secondary endpoints included toxicity, progression-free survival (PFS) and overall survival, as well as clinical benefit response in symptomatic patients.
Results Forty patients from two institutions were enrolled between September 2004 and November 2005. The most common adverse reactions were fatigue and anorexia, although most of those adverse reactions were tolerable and reversible. One patient developed grade 3 pneumonitis without neutropenia and recovered with appropriate antibiotic treatment. Although no complete response was seen, partial response was obtained in six patients (15, 95% confidence interval, 3.9–26%). Stable disease was noted in 17 patients (43%), and progressive disease in 15 patients (38%). Out of 19 evaluable patients, a clinical benefit response was observed in four patients (21%). The median PFS was 2.0 months, and the median survival time was 4.5 months with a 1-year survival rate of 14.1%.
Conclusion S-1 as monotherapy had marginal anti-tumor activity with tolerable toxicity in patients with gemcitabine refractory metastatic pancreatic cancer.

Keywords Chemotherapy · Pancreatic carcinoma · Second-line · Salvage

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Background

The prognosis of patients with pancreatic carcinoma is extremely poor because of difficulty in the early detection of this disease, the high incidence of postoperative recurrence, and ineffectiveness of nonsurgical treatments. Gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU [3]. However, the benefit provided was inadequate, with an objective response rate of less than 15% and a median survival of 5–7 months. To improve the prognosis of patients with pancreatic cancer, one of the strategies is to develop the effective first-line chemotherapy including

gemcitabine combinations. Among various combinations with gemcitabine plus other agents as a first-line chemotherapy, only a few regimens have shown any survival benefit over single-agent gemcitabine [6, 20, 25], although the worldwide consensus regarding the results of these studies has not been established. Another strategy is to develop an effective second-line chemotherapy regimen after disease progression during first-line chemotherapy. However, despite the fact that several studies have investigated second-line chemotherapy in pancreatic cancer, the therapeutic results have been disappointing with poor response rate and survival [1, 2, 4, 5, 7, 14, 16, 18, 19, 21, 26, 27, 33, 34, 36, 38] Effective treatment in patients failing gemcitabine-based chemotherapy is eagerly awaited.

S-1 is a novel orally administered drug that is a combination of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and oteracil potassium (Oxo) in a 1:0.4:1 molar concentration ratio [31]. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and acts to maintain efficacious concentrations of 5-FU in plasma and tumor tissues [35]. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract, reducing the serious gastrointestinal toxicity associated with 5-FU [32]. The antitumour effect of S-1 has already been demonstrated in a variety of solid tumors such as advanced gastric cancer [15, 30], colorectal cancer [23], non-small-cell lung cancer [13], head and neck cancer [11], and breast cancer [29].

Concerning pancreatic cancer, a recent late phase II study of S-1 for chemo-naïve advanced pancreatic cancer patients demonstrated promising results with a response rate of 37.5% and a favorable toxicity profile [24]. Furthermore, clinical studies have reported activity of gemcitabine in pancreatic cancer patients with refractoriness to 5-FU [28], suggesting the lack of crossresistance between the gemcitabine and fluorinated pyrimidine, including S-1. Therefore, we conducted the present phase II study to investigate the feasibility and efficacy of S-1 in patients with advanced pancreatic adenocarcinoma in a progressive state under gemcitabine-based first-line chemotherapy.

Patients and methods

Patients

All patients were required to show histologically proven pancreatic adenocarcinoma with measurable metastatic lesions. Additional criteria included the following: progressive disease under gemcitabine-based first-line chemotherapy, post operative recurrence or metastatic disease before the start of first-line chemotherapy, 20–74 years of age, Karnofsky performance status (KPS) of 80–100 points, more than 3 weeks intervals between the last administration of the prior chemotherapy regimen and study entry, adequate bone marrow function (white blood cell count $\geq 3{,}000/mm^3$, neutrophil count $\geq 1500/mm^3$, platelet count $\geq 100{,}000/mm^3$, haemoglobin level ≥ 9.0 g/dl), adequate renal function (serum creatinine level ≤ 1.5 mg/dL), and adequate liver function (serum total bilirubin level ≤ 2.0 mg/dL, transaminases level ≤ 2.5 times the upper limits of normal). Patients who had obstructive jaundice or liver metastasis were considered eligible if their transaminases levels could be reduced to within 5 times the upper normal limit of normal after biliary drainage. The exclusion criteria were as follows: regular use of phenytoin, warfarin or frucitocin, history of fluorinated pyrimidine use, severe mental disorder, active infection, ileus, interstitial pneumonia or pulmonary fibrosis, refractory diabetes mellitus, heart failure, renal failure, active gastric or duodenal ulcer, massive pleural or abdominal effusion, brain metastasis, active concomitant malignancy. Pregnant or lactating women were also excluded. Written informed consent was obtained from all patients. This study was approved by the institutional review board at the National Cancer Center in Japan.

Treatments

S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily after breakfast and dinner. Three initial doses were established according to the body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 m$^2 \leq$ BSA < 1.50 m^2, 100 mg/day; and 1.50 m$^2 \leq$ BSA, 120 mg/day. S-1 was administered at the respective dose for 28 days, followed by a 14-day rest period; this treatment course was repeated until the occurrence of disease progression, unacceptable toxicities, or the patient's refusal to continue. When a grade 3 or greater haematologic or grade 2 or greater nonhaeamatologic toxicity occurred, either the temporary interruption of the S-1 administrations until the toxicity decreased to grade 1 or less, or dose reduction by 20 mg/day (minimum dose, 80 mg/day) was recommended. If no toxicity occurred, the rest period was shortened to 7 days or the dose was gradually escalated in the next course (maximum dose, 150 mg/day), or both were permitted according to the judgment of the individual physicians. If a rest period of more than 28 days was required because of toxicity, the patient was withdrawn from the study. Patients were not allowed to receive concomitant radiation therapy, chemotherapy, or hormonal therapy during the study. Patients maintained a daily journal to record their intake of S-1 and any signs or symptoms that they experienced.

Response and toxicity evaluation

The response after each course was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Primary pancreatic lesions were not considered to be measurable lesions because the dimensions of such lesions are difficult to measure accurately. Physical examinations, complete blood cell counts, biochemistry tests, and urinalyses were performed at least weekly. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Clinical benefit response

The clinical benefit response (CBR) was evaluated using the KPS and pain score, as described below [3]. The KPS was recorded weekly by the attending physician. Pain was evaluated by measuring the change from the baseline pain intensity and the daily dose of morphine or morphine-equivalent (doses of analgesic agents were converted to morphine-equivalent doses, i.e., 10 mg oxycodone = 15 mg morphine). The pain intensity was graded from 0 (no pain) to 100 (worst pain) using a visual analog scale and was recorded on a pain assessment card every day. Patients who fulfilled at least one of the following criteria were defined as eligible CBR analysis: (1) baseline pain intensity $\geq$20, or (2) baseline morphine consumption $\geq$10 mg/day. Moreover, all the patients underwent a 'pain stabilization period' for 2 days to ensure that the baseline values were stable before treatment: when the variation in the morphine consumption between 2 days was within 10 mg and the variation of the pain intensity was within 20, the patient was considered eligible for inclusion in the CBR analysis. For pain intensity, a positive response occurred when the score was improved by $\geq$50% from baseline, sustained for $\geq$4 weeks. For analgesic consumption, a positive response occurred when the weekly consumption was reduced by $\geq$50% from baseline, maintained for $\geq$4 weeks. A positive response for KPS was defined as an improvement of $\geq$20 points from baseline, sustained for at least 4 weeks. Any worsening from baseline, sustained for 4 weeks, was considered a negative response for each of the three domains. All the other results were considered stable. Pain intensity and analgesic consumption were compared to give a composite pain score. Each patient was classified positive, stable or negative for each of the primary measures (pain and KPS). In order to achieve a positive clinical benefit response, patients had to be positive for at least one parameter without being negative for any of the others for a minimum of 4 weeks. Patients who were stable in the two primary measures were classified as stable.

Statistical design

The primary endpoint of this study was objective response rate. The secondary endpoint of this study was clinical benefit response; toxicity; progression-free survival; and survival. The number of patients to be enrolled was planned using a SWOG's standard design (attained design) [8, 9]. The null hypothesis was that the overall response rate would be $\leq$5% and the alternative hypothesis was that the overall response rate would be $\geq$20%, the α error was 5% (one-tailed) and the β error was 10% (one-tailed). The alternative hypothesis was established based on the preferable data from previous reports [7, 16, 27, 36, 38]. Interim analysis was planned when 20 patients were enrolled. If none of the first 20 patients had a partial response or complete response, the study was to be ended. If a response was detected in any of the first 20 patients studied, an additional 20 patients were to be studied in a second stage of accrual to estimate more precisely the actual response rate. If the lower limit of the 90% confidence interval exceeded the 5% threshold (objective response in seven or more of the 40 patients), S-1 was judged to be effective and we would proceed to the next large-scale study.

The progression-free survival was calculated from the date of study entry to the date of documented disease progression or death due to any cause (whichever occurred first); and overall survival time was calculated from the date of study entry to the date of death or the last follow-up. The median probability of the survival period and progression-free survival were estimated using the Kaplan–Meier method. The relative dose intensity of S-1 was calculated according to the Hryniuk method [10].

Results

Patients

Forty consecutive patients with metastatic pancreatic cancer which was progressing under gemcitabine-based first-line chemotherapy were enrolled in this study between September 2004 and November 2005. The patient characteristics are shown in Table 1. Thirty-six of the forty patients showed a KPS of $\geq$90. Prior treatment was gemcitabine monotherapy in all patients. Thirty-six of the forty patients (90%) received gemcitabine as a standard 30 min infusion, and the remaining four patients (10%) received gemcitabine administered by fixed dose rate infusion. Of 40 patients, 4 patients (10%) showed a partial response, 21 patients (53%) showed stable disease, and 12 (30%) patients showed progressive disease in first-line gemcitabine therapy. Three patients had received first-line chemotherapy at another hospital and accurate data about

Table 1 Patient characteristics ($n = 40$)

Age	
Median (range)	62 (36–74)
Gender	
Male	21
Female	19
KPS	
100	17
90	19
80	4
Biliary drainage	
(+)	6
Prior pancreatectomy	
(+)	7
Location of primary tumor	
Head	17
Body	14
Tail	9
Sites of metastasis	
Liver	33
Lymph node	16
Lung	3
Peritoneum	4
Prior chemotherapy	
Gemcitabine[a]	36
FDR-GEM[b]	4
TTP of prior treatment (months)	
Median (range)	2.8 (0.7–13.5)
CEA (ng/ml)	
Median (range)	14.9 (1.1–1,187)
CA19-9 (U/ml)	
Median (range)	4,673 (0.1–2,960,000)

KPS Karnofsky performance status, *TTP* time to progression, *CEA* carcinoembryonic antigen, *CA 19-9* carbohydrate antigen 19-9

[a] Gemcitabine as a standard 30-min infusion

[b] FDR-GEM: gemcitabine as a fixed dose rate infusion

treatment response could not be obtained. The median time to progression in the prior treatment was 2.8 months (range 0.7–13.5 months).

Treatments

A total of 94 courses were administered to the 40 patients with a median of two courses per patient (range 1–12). The initial administered dose of S-1 was 80 mg/day in 1 patient, 100 mg/day in 18 patients, and 120 mg/day in 21 patients. Treatment interruption was necessary in 18 patients, due to fatigue (grade 3: one patients, grade 2: one patient, grade 1: two patients), nausea (grade 2: three patients, grade 1: one patient), diarrhea (grade 3: two patients, grade 1: two patients), drainage tube related problem (two patients), grade 3 appetite loss (1), grade 1 leukocytopenia (1), grade 2 hand-foot skin reaction (1), and grade 1 pneumonitis (1). Dose reduction was required in three patients because of grade 3 diarrhea (1), grade 2 fatigue (1), and grade 1 nausea (1). The relative dose intensity was 94.7%. The reasons for discontinuation of treatment were radiologically confirmed progressive disease (PD) in 31 patients, clinical PD without radiological PD in 6 patients, at the patients request due to unacceptable toxicities in 2 patients (grade 2 fatigue and grade 3 anorexia), and loss to follow up in one patient.

Toxicity

All 40 eligible patients were assessable for adverse events. The treatment-related adverse reactions are listed in Table 2. One patient developed grade 3 pneumonitis without neutropenia and required hospitalization, but she recovered from the pneumonitis with antibiotic treatment. As to other grade 3 non-hematological toxicities, aspartate aminotransferase elevation (two patients), alanine aminotransferase elevation (2), fatigue (2), anorexia (2), diarrhea (2) were noted. Regarding hematological toxicities, grade 3 anemia was noted in one patient. No other severe or unexpected adverse reactions were noted. The most common adverse reactions were fatigue (78%) and anorexia (73%), although most of those adverse reactions were tolerable and reversible. Although five patients died within 4 weeks after discontinuation of treatment due to rapid disease progression, no treatment-related deaths were observed.

Efficacy

Out of the total of 40 eligible patients, 38 patients were assessable for response. Two patients discontinued chemotherapy at their request due to unacceptable toxicities (grade 2 fatigue and grade 3 anorexia) and moved to another hospital before tumor assessment. Although no complete response was seen, partial response was obtained in six patients (15, 95%, confidence interval 3.9–26%). Stable disease was noted in 17 patients (43%), and progressive disease in 15 patients (38%). Tumor responses to second-line S-1 therapy are classified according to tumor responses to first-line gemcitabine in Table 3. The serum CA 19-9 level was reduced to less than half in 8 (23%) of 35 patients with a pretreatment serum CA19-9 level of the upper limit of normal or greater. At the time of enrollment, nineteen of forty (47.5%) patients were eligible for the evaluation of clinical benefit response. Out of nineteen evaluable patients, a clinical benefit response was observed in four patients (21%). The median progression free survival time was 2.0 months, and the median survival time was 4.5 months (range 1.2–14.3+) with a 1-year survival rate of 14.1% (Fig. 1).

Table 2 Treatment-related adverse events ($n = 40$): worst grade reported during treatment period

	Grade				Grade 1–4	Grade 3–4
	1	2	3	4	*n* (%)	*n* (%)
Hematological toxicity						
Leukocytes	8	2	0	0	10 (25)	0 (0)
Neutrophils	3	2	0	0	5 (13)	0 (0)
Hemoglobin	5	13	1	0	19 (48)	1 (3)
Platelets	9	0	0	0	9 (23)	0 (0)
Non-hematological toxicity						
Aspartate aminotransferase elevation	13	1	2	0	16 (40)	2 (5)
Alanine aminotransferase elevation	8	1	2	0	11 (28)	2 (5)
Total bilirubin elevation	4	3	0	0	7 (18)	0 (0)
Fatigue	21	8	2	0	31 (78)	2 (5)
Nausea	18	6	0	0	24 (60)	0 (0)
Vomiting	5	1	0	0	6 (15)	0 (0)
Anorexia	22	5	2	0	29 (73)	2 (5)
Stomatitis	11	3	0	0	14 (35)	0 (0)
Diarrhea	8	4	2	0	14 (35)	2 (5)
Rash	3	0	0	0	3 (8)	0 (0)
Pigmentation	6	1	–	–	7 (18)	–
Hand-foot skin reaction	1	1	0	–	2 (5)	0 (0)
Pneumonitis without neutropenia	0	0	1	0	0 (0)	1 (3)

Table 3 Objective tumor response (RECIST criteria) ($n = 40$)

Response (2nd line)	*n* (%)	Response (1st line)			
		PR	SD	PD	NE
CR	0 (0%)	0	0	0	0
PR	6 (15%)	1	4	0	1[a]
SD	17 (43%)	2	9	5	1[a]
PD	15 (38%)	1	6	7	1[a]
NE	2 (5%)	0	2	0	0
Total	40 (100%)	4	21	12	3

Treatment response to second-line S-1 therapy is tabulated according to treatment response to first-line gemcitabine

[a] Three patients received first-line chemotherapy at another hospital and accurate data about treatment ressponse was unobtainable

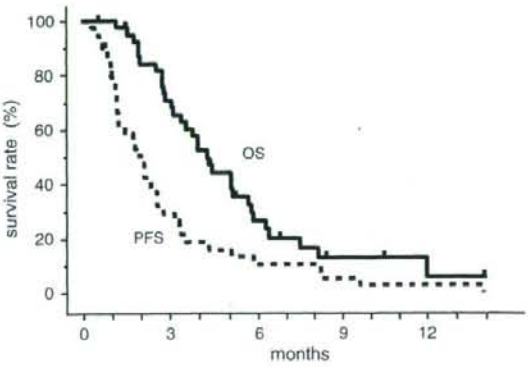

Fig. 1 Survival ($n = 40$). Progression free survival (*dashed line*), and overall survival time (*solid line*) curves of patients with gemcitabine refractory pancreatic cancer receiving systemic chemotherapy with S-1

Discussion

Over the last several years, many studies have been designed to establish effective treatment for gemcitabine-refractory pancreatic cancer patients. So far, the results of two randomized phase III studies had been reported. Jacobs et al. reported on a phase III study comparing Rubitecan, a new topoisomerase I inhibitor, versus "physicians' choice" in 409 pretreated patients. The study was unable to indicate any statistically significant survival benefit in the Rubitecan arm (3.7 months vs. 3.1 months, $P = 0.626$), although progression-free survival was significantly improved in Rubitecan arm (1.9 months vs. 1.6 months, $P = 0.001$) [12]. On the other hand, Oettle et al. [22] reported on phase III study comparing a combination of oxaliplatin, 5-FU and folinic acid with best supportive care (BSC). The BSC arm closed to accrual after 46 out of 165 planned patients were enrolled because physicians deemed it unethical. The median survival of second-line therapy was 21 weeks compared to 10 weeks for the BSC group ($P = 0.0077$). However, a worldwide consensus regarding this result has not been established because of the small number of patients in

this study. Other studies have investigated the feasibility and activity of second-line treatments in phase II studies [1, 4, 7, 17, 19, 26, 27, 33, 36, 38]. Compared with monotherapy, combination regimens exhibited superior activity in these studies. Fluoropyrimidine-, Irinotecan- or oxaliplatin-based combinations indicated relatively preferable activity with objective responses rate of about 20% and a median survival of 5–6 months in this setting [7, 17, 27, 36, 38]. The safety profiles of such combination regimens require further careful evaluation, and well-designed, larger randomized controlled studies are needed.

In the current study, S-1 produced a response rate of 15%, which was superior to the rates obtained for other reported single agents, including paclitaxel (5.5%) [21], raltitrexed (0%) [38], rubitecan (7%) [4]. However, this response rate failed to reach the pre-established boundary of 17.5% required for the agent to be considered effective. Furthermore, the progression-free survival (median 2 months) and the overall survival (median 4.5 months) were still extremely poor in this study. Although S-1 seems to have some degree of anti-tumor activity in patients with gemcitabine refractory metastatic pancreatic cancer, monotherapy may be insufficient to prolong survival. This limitation may be due to the strong chemo-resistance and heterogeneity of the tumors caused by the nature of the disease and acquired from previous chemotherapy regimens.

The toxicity of S-1 was acceptable and no life-threatening toxicities were observed. Although a population with an extremely poor prognosis was targeted in this study and the general condition of the participating patients was expected to be unstable, the toxicities were similar to the results of previous clinical studies for S-1 in chemo-naïve patients with pancreatic cancers [24, 37]. The safety profile of this study suggests that S-1 can be safely administered to pancreatic cancer patients even in a second-line setting, at least in selected populations.

We conclude that S-1 as monotherapy had marginal anti-tumor activity with tolerable toxicity in patients with gemcitabine refractory metastatic pancreatic cancer. In view of the favorable toxicity profile, its combination with other agents might have potential to improve therapeutic results.

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Original Paper

Phase II Study of Cisplatin, Epirubicin and Continuous Infusion of 5-Fluorouracil in Patients with Advanced Intrahepatic Cholangiocellular Carcinoma (ICC)

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KEY WORDS:
Cisplatin; Epirubicin; 5-Fluorouracil; Chemotherapy; Intrahepatic cholangiocellular carcinoma

ABBREVIATIONS:
5-Fluorouracil (5FU); Intrahepatic Cholangiocellular Carcinoma (ICC); Computed Tomography (CT); Biliary Tract Cancer (BTC); ECOG: Eastern Cooperative Oncology Group; Intravenous (IV)

ABSTRACT

Background/Aims: To clarify the efficacy and toxicity of cisplatin, epirubicin, and continuous infusion of 5-FU (CEF therapy) in patients with advanced intrahepatic cholangiocellular carcinoma (ICC).

Methodology: Chemo-naïve patients with advanced ICC were treated with cisplatin at 80mg/m² and epirubicin at 50mg/m² on day 1, and continuous infusion of 5-FU at 500mg/m²/day on days 1 through 5. If there was no evidence of tumor progression or unacceptable toxicity, the treatment was repeated every 4 weeks, up to a maximum of 6 courses.

Results: Thirty-nine patients were enrolled in this study. The median number of courses was 2 (range, 1-6). A partial response was obtained in 4 patients (10%) with a median duration of 2.3 months. Twenty-seven patients (69%) showed no change, and 7 patients (18%) had progressive disease. The median survival time was 9.1 months and the 1-year survival rate was 23%. The progression-free survival time was 5.1 months. Grade 3 to 4 adverse effects were leukocytopenia (51%), neutropenia (74%), thrombocytopenia (23%), and nausea/vomiting (10%). Most of the toxicities were reversible, but 2 patients died of neutropenic sepsis.

Conclusions: CEF therapy has marginal antitumor activity against advanced ICC, although hematological toxicity is the major and most frequent toxicity.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a rare malignancy accounting for approximately 3.3% of primary malignant liver tumor in Japan (1). ICC is difficult to diagnose, with most patients surgically unresectable at the time of diagnosis. Moreover, even for those who undergo surgical resection, the risk of recurrence is exceedingly high, and the overall prognosis remains unsatisfactory. To improve the prognosis of patients with this disease, effective chemotherapy is essential, but standard chemotherapy for ICC has not been established. Furthermore, few disease-oriented studies of chemotherapy for ICC have been reported because of the low incidence of this disease.

The authors of the present study previously reported that cisplatin did not appear active as a single agent in treating patients with biliary tract cancer (BTC) including ICC; the response rate of this agent was only 8% (1/13), but a 50% or more reduction in the CEA level was obtained in 31% of patients (3). The activity of cisplatin is potentiated by certain other anticancer agents such as 5-FU (4,5). In addition, anthracyclines may enhance the cytotoxicity afforded by combining cisplatin and 5-FU (6). In fact, continuous infusion of 5-FU with cisplatin and epirubicin has been reported to be an active regimen in the management of gastrointestinal cancers such as gastroesophageal cancer (7-10). However, it appears that this combined treatment has not been evaluated in patients with ICC. Therefore, in this phase II study, the efficacy and toxicity of cisplatin, epirubicin, and continuous infusion of 5-FU (CEF therapy) in patients with unresectable ICC, was investigated.

METHODOLOGY

Patients

Patients eligible for this study had histologically confirmed unresectable advanced intrahepatic cholangiocarcinoma for which they had not had prior irradiation or chemotherapy. Each patient was required to meet the following eligibility criteria: an ECOG performance status (PS) of 0-2; 15-75 years of age; at least 1 bidimensionally measurable tumor; estimated life expectancy ≥8 weeks after study entry; adequate renal function (normal serum creatinine and blood urea nitrogen levels); adequate liver func-

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tion (total bilirubin level ≥3.0mg/dL); and adequate bone marrow reserve (white blood cell count ≥4,000/μL, platelet count ≥100,000/μL, hemoglobin ≥11g/dL). Patients with an elevated serum bilirubin level at the time of pretherapy evaluation were considered eligible for this study if the bilirubin level could be reduced to within 3.0mg/dL after biliary drainage. All patients were required to provide written informed consent.

Exclusion criteria were as follows: uncontrollable pleural effusion or ascites; known metastases of the central nervous system; gastrointestinal bleeding; severe complications such as infection, heart disease, and renal disease; active concomitant malignancy; severe mental disorder; and pregnancy.

Treatment schedule

All therapies were administered on an in-patient basis. 5-FU was administered by continuous intravenous (IV) infusion at a dose of 500mg/m² on days 1 through 5. Epirubicin was administered by IV infusion at a dose of 50mg/m² on day 1, and cisplatin was administered by IV infusion at a dose of 80mg/m² over a 2-h period on day 1 with standard hydration. The dose of epirubicin was adjusted to the hematological toxicities observed; patients who experienced grade 4 leukocytopenia and/or neutropenia received 40mg/m² in subsequent courses. If there was no evidence of tumor progression or unacceptable toxicity, the treatment was repeated every 4 weeks, to a maximum of 6 courses.

Response and toxicity evaluation

Tumor size was measured by computed tomography (CT), and tumor response was assessed every 4 weeks after the beginning of chemotherapy. Response and toxicity were evaluated according to the World Health Organization guidelines (11).

Statistical Design

The primary endpoint was the efficacy and toxicity of CEF therapy in patients with advanced ICC. The number of patients to be enrolled was planned using a Simon's two-step design (12), based on the assumptions that the expected response rate would be 20%, the response rate judged as no activity would be 5%, alpha error would be 10% (one-tailed), and β error would be 10% (one-tailed).

Interim analysis was planned when 12 patients were enrolled. If none of the first 12 patients had a partial or complete response, the study was to be ended. If a response was detected in any of the first 12 patients studied, an additional 25 patients were to be studied in a second stage of accrual to estimate more precisely the actual response rate. The time to progression and survival time were also calculated from the start of treatment by the Kaplan-Meier method.

RESULTS

Thirty-nine patients were enrolled in this study at the National Cancer Center Hospital between May 1992 and November 2001. Patient characteristics are summarized in **Table 1**.

TABLE 1 Patient Characteristics

No. of patients		39
Sex	Men	25
	Women	14
Age (yrs)	Median (range)	60 (37-75)
ECOG PS	0	19
	1	20
Metastatic organ	Lymph node	14
	Lung	10
Prior surgery +		13
Biliary drainage +		5
Albumin (g/dl)	Median (range)	3.7 (2.6-4.5)
Total bilirubin (mg/dl)	Median (range)	0.8 (0.3-3.0)
CEA (ng/ml)	Median (range)	3 (0.8-7100)
CA19-9 (U/ml)	Median (range)	109 (1-382720)

ECOG: Eastern Cooperative Oncology Group; PS: performance status; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

All patients had histologically confirmed adenocarcinoma. The population consisted of 25 men and 14 women with a median age of 60 yrs (range: 37-74). Before chemotherapy, 13 patients had undergone prior hepatic resection and 5 patients had undergone biliary drainage for obstructive jaundice. All patients were deemed unsuitable candidates for surgical resection for one of the following reasons: extrahepatic metastasis (14 patients), huge tumor extending across the bilobes of the liver (12 patients), or intrahepatic recurrence after hepatic resection (13 patients).

The 39 patients were given a total of 127 courses, with a median of 3 courses each (range: 1-6; **Table 2**). The dose of epirubicin was modified to 40mg/m² according to the protocol in 9 patients (23%). The reasons for treatment discontinuation were: completion of treatment (6 courses) (8 patients, 21%); disease progression (26 patients, 67%); patient's refusal of treatment (1 patient, 3%); and treatment-related death (2 patients, 5%).

Thirty-eight patients were evaluable for response. One patient was evaluable for toxicity alone but not for response because she died due to treatment-related sepsis before the response evaluation. No complete

TABLE 2 Number of Treatment Courses

Courses	Number of patients (%)
1	9 (23)
2	8 (21)
3	7 (18)
4	4 (10)
5	3 (7)
6	8 (21)

TABLE 3 Toxicity

Grade	1	2	3	4
Hematological toxicity				
Per patient				
Hemoglobin	11 (28%)	14 (36%)	1 (3%)	1 (3%)
Leukocytes	7 (18%)	7 (18%)	16 (41%)	4 (10%)
Neutrophils	0 (0%)	2 (5%)	13 (33%)	16* (41%)
Platelets	10 (26%)	2 (5%)	7 (18%)	2 (5%)
Non-hematological toxicity				
Per patient				
Gastrointestinal				
Total bilirubin	8 (21%)	0 (0%)	0 (0%)	1 (3%)
AST	12 (31%)	4 (10%)	0 (0%)	0 (0%)
ALT	6 (15%)	4 (10%)	3 (8%)	0 (0%)
ALP	6 (15%)	8 (21%)	3 (8%)	0 (0%)
Renal/Genitourinary				
BUN	2 (5%)	2 (5%)	0 (0%)	0 (0%)
Creatinine	3 (8%)	1 (3%)	0 (0%)	0 (0%)
Nausea/Vomiting	18 (46%)	9 (23%)	2 (5%)	2 (5%)
Stomatitis	19 (49%)	4 (10%)	0 (0%)	0 (0%)
Diarrhea	5 (13%)	1 (3%)	0 (0%)	0 (0%)
Infection	8 (21%)	3 (8%)	0 (0%)	3 (8%)
Malaise/Fatigue	17 (44%)	11 (28%)	5 (13%)	1 (3%)

*Two patients died of neutropenic sepsis.
AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; BUN: blood urea nitrogen.

response was noted. A partial response was obtained in 4 patients (10%, 95% CI: 3-24%) with a median duration of 2.3 months (range: 1–8 months). Twenty-seven (69%) patients showed no changes, with a median duration of 7.8 months (range: 1-19 months). Seven patients (18%) showed progressive disease.

Toxicities are listed in **Table 3**. CEF therapy was generally well tolerated although 2 patients died of neutropenic sepsis, on day 10 of the 3rd course and on day 27 of the 1st course, respectively. Grade 4 leukocytopenia, neutropenia and thrombocytopenia occurred in 4 (10%), 16 (41%) and 2 (5%) patients, respectively. However, these toxicities were generally brief and reversible. Anemia was infrequent and mild. No cumulative tendency of myelosuppression was noted as the treatment courses continued. Severe non-hematological toxicities of CEF therapy were infrequent, and nausea/vomiting and malaise were the most common non-hematological toxicities.

All enrolled patients were included in the survival assessment. Thirty-six patients had died, and 3 patients were alive at the time of analysis. The median survival time was 9.1 months (range: 0.9-40.7 months) and the 1-year survival rate was 23% (**Figure 1**). The progression-free survival time was 5.1 months.

DISCUSSION

Hepatobiliary cancer is one of the most common malignancies in Japan. The annual incidence of hepatobiliary cancer has been steadily increasing in this nation, from 15.8 per 100,000 in the year 1989 to 18.2 per 100,000 in 1999 (2). ICC is, however, a rare malignancy accounting for approximately 3.3% of all primary hepatobiliary malignancies and 0.03% of all cancers in Japan (1). Due to the rarity of ICC, it is not surprising that there have been few prospective trials of systemic chemotherapy for ICC.

Gemcitabine is the only chemotherapeutic agent that has been evaluated in a disease-oriented study for ICC. In a phase II trial, the objective response rate was 30% (7/15) with a median time to tumor progression of 6.8 months and a median survival time of 9.3 months (20). Other chemotherapeutic agents have been investigated for BTC including cancers of the gallbladder and the intra- and extra-hepatic bile duct. 5-FU has been the most extensively studied single agent for this disease, with published objective response rates ranging from 10 to 24% (13-15). Mitomycin C has also been a commonly studied drug for BTC; a phase II study conducted by Crooke *et al.* showed a response rate of 47% (7/15) (16). However, a study by the European Organization for Research and Treatment of Cancer, testing mitomycin C in 30 patients showed only 3 (10%) responses (17). Some newer drugs have also demonstrated no significant efficacy as a single-agent therapy. Paclitaxel demonstrated no activity in 15 patients (18), and a phase II study of docetaxel likewise demonstrated no activity in 17 patients (19). Therefore, no single agent has reproducibly induced a sufficient antitumor response against BTC including ICC.

Due to the rather sobering results obtained with single-agent chemotherapy, various combination chemotherapies have been investigated in order to enhance response and to prolong survival in patients with BTC (21-30). In an ECOG study, 8 (9%) of the 89 patients showed a response in 5-FU-based chemotherapy using oral 5-FU or oral 5-FU plus either streptozotocin or methyl-CCNU. There were no significant differences in the types of drugs used with respect to response and survival (15). Recombinant interferon-α, which is a potent biochemical modulator of 5-FU, was tested in combination with 5-FU for 41 patients, and 8 patients (21%) achieved an objective response (22). However, the addition of cisplatin and adriamycin to the combination of 5-FU and interferon-α did not enhance antitumor activity: only 2 (14%)

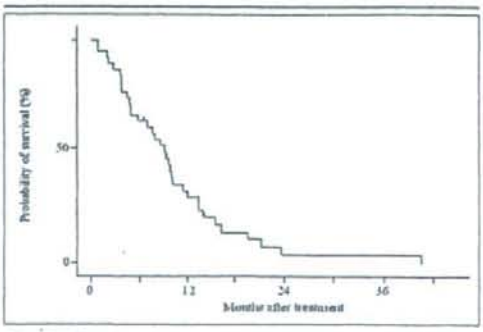

FIGURE 1 Overall survival curve of the 39 patients who received CEF therapy for ICC.

of the 14 patients showed an objective response in a recent phase II study (23). The combination of 5-FU, mitomycin C, and doxorubicin has also been evaluated: one study analyzing this combination for 13 patients showed 4 partial responses (3 %) (24). Conversely, in a more recent trial in 14 patients, a modified regimen using these three agents demonstrated only 2 (14%) objective responses (25). A combination chemotherapy of epirubicin, methotrexate, and 5-FU showed no responses in 21 patients (26). For patients with advanced BTC including ICC, there is currently no standard chemotherapy.

Cisplatin has also been attempted, alone or in combination, in clinical trials for patients with BTC. One report showed 6 partial responses (33%) in 18 patients treated with continuous-infusion 5-FU and cisplatin (27). In another report, the addition of leucovorin to the combination of 5-FU and cisplatin showed 1 complete response and 9 partial responses (34%) in 21 patients (28). The activity of CEF therapy in hepatobiliary cancers has been reported in two phase II studies. In an English trial that was conducted for hepatobiliary cancers including ICC, partial response was achieved in 8 (40%) of the 20 patients, with a median survival time of 11 months (29). In another trial that was conducted in our hospital for BTC other than ICC, the results showed 7 partial responses (19%) in the 37 patients (30). These results suggest that 5-FU-based chemotherapy including cisplatin may have a favorable antitumor effect against BTC.

Our current study is the first disease-specific phase II trial for ICC treated with multi-agent chemotherapy including cisplatin. However, the results of the present study were very disappointing. This study failed to demonstrate significant antitumor activity; only 4 patients (10%) achieved a partial response, although the expected response rate was 20%. Although the CEF therapy was generally well tolerated, grade 3/4 myelotoxicity was frequent. Grade 4 neutropenia was noted in 16 patients (41%), and 2 of them died of sepsis caused by pneumonia. Nausea/vomiting and malaise were the most common non-hematological toxicities, and grade 3/4 nausea/vomiting was noted in 4 patients (10%). Grade 4 bilirubin elevation was noted in 1 patient (3%), who was diagnosed as having biliary pyogenic cholangitis caused by drainage tube obstruction. Grade 3 liver dysfunction was observed in 3 patients (8%), but their liver functions recovered to initial levels within 2 weeks.

ICC can be one of the most difficult cancers to treat effectively with chemotherapy, given the rapid progressive and chemoresistant nature of this disease. In the patients with BTC treated with CEF in the England trial, only 2 of the 9 patients with cholangiocarcinoma (22%) achieved a response, while 6 of the 11 patients with other BTC (55%) responded.

The conclusion of the current study is that CEF therapy has only marginal antitumor activity against advanced ICC, although hematological toxicity is the major and most frequent toxicity. Therefore, this regimen may not be adequate for recommendation as a standard. Further studies with new agents including gemcitabine are needed, and the expanding understanding of molecular biology should facilitate research to develop novel target-based agents for this disease.

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