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Early Phase II Study of Uracil–Tegafur Plus Doxorubicin in Patients with Unresectable Advanced Biliary Tract Cancer

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Background: Standard chemotherapy for advanced biliary tract cancer has not been established. The purpose of this study was to evaluate the efficacy and toxicity of a combination chemotherapy of uracil–tegafur (UFT) and doxorubicin in patients with unresectable advanced biliary tract cancer.

Methods: Patients with histologically or cytologically confirmed, measurable biliary tract cancer, including intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer and ampulla of Vater cancer, which was not amenable to surgery, were eligible for the study. Patients received oral UFT 300 mg/m^2 per day divided into two doses on Days 1–14 and intravenous doxorubicin 30 mg/m^2 on Day 1. This cycle was repeated every 21 days. Additional courses of this regimen were given until a maximum of 15 courses, disease progression or the appearance of unacceptable toxicity.

Results: Twenty-four patients from five institutions were enrolled between March 2004 and November 2004. Of the 24 patients, three had partial responses for an objective response rate of 12.5% (95% confidence interval, 2.7–32.4%), 13 patients had stable disease, 7 had progressive disease and the final patient was not evaluated. Grade 3 toxicity was observed in 5 of the 24 patients (20.8%), and these toxicities included anorexia, fatigue, anemia and neutropenia. None had grade 4 toxicity. The median progression-free and overall survival time was 2.5 and 7.6 months, respectively.

Conclusions: Combination chemotherapy of UFT and doxorubicin was well tolerated and showed preliminary moderate activity against advanced biliary tract cancer. Further investigation in a late phase II study involving a large number of patients is recommended.

Key words: advanced biliary tract cancer – systemic chemotherapy – uracil–tegafur – doxorubicin

INTRODUCTION

Biliary tract cancer is one of the common causes of cancer death in Japan, with an estimated 16 000 deaths annually (1). Although surgery currently remains the only potentially curative treatment, most patients are found to have an unresectable advanced stage of disease. The curative resection rates for gallbladder cancer range from 10 to 30% (2,3). Although patients with unresectable disease receive various palliative treatments, including systemic chemotherapy, the prognosis remains extremely poor.

A previous report showed improved survival in patients with biliary tract cancer with 5-fluorouracil (5-FU)-based chemotherapy compared with the best supportive care (4). Efforts have been made to develop promising regimens for biliary tract cancer using clinical trials of systemic chemotherapy (5). In various reports on chemotherapy for biliary tract cancer, fluoropyrimidines have been considered as the basis of chemotherapy (5–8). Furthermore, cisplatin or anthracycline antitumor antibiotic agents such as doxorubicin and epirubicin have been used as combination chemotherapy with 5-FU (9–12). However, no standard chemotherapy has currently been identified that can clearly prolong survival.

In Japan, only three anticancer agents—uracil–tegafur (UFT), doxorubicin, and cytarabine—are strictly approved

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by the Ministry of Health, Labor, and Welfare for biliary tract cancer. UFT is an orally administered drug that is a combination of uracil and tegafur in a 4:1 molar concentration ratio. Tegafur is a 5-FU prodrug that is hydroxylated and converted to 5-FU by hepatic microsomal enzymes. Uracil prevents degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase, which leads to an increased level of 5-FU in plasma and tumor tissues (13,14). Doxorubicin is an anthracycline antibiotic that induces various biological effects and has one of the widest spectra of antitumor activity against lymphomas, leukemias, soft tissue sarcomas and a variety of carcinomas. However, in previous reports (15–17), UFT had little activity or doxorubicin was not examined enough as a single agent in treating patients with advanced biliary tract cancer. Cytarabine has not been applied for biliary tract cancer.

Some regimens that include a combination of a fluoropyrimidine and an anthracycline antibiotic, such as the FAM regimen (5-FU, doxorubicin, and mitomycin) and the CEF, regimen (cisplatin, epirubicin, and 5-FU), showed moderate activity (9–12). A combination of a fluoropyrimidine and an anthracycline antibiotic should have some efficacy against biliary tract cancer, but no such regimen has ever been assessed. Since UFT+doxorubicin is the only doublet regimen currently covered by health insurance in Japan, we conducted an early phase II study to evaluate the antitumor activity and toxicity of this combination (the UFD regimen) in patients with unresectable advanced biliary tract cancer. The objectives of this study were to evaluate response rate, toxicity, progression-free survival and overall survival.

PATIENTS AND METHODS

Patients Eligibility

Eligibility criteria for enrollment in the study were: (i) histologically or cytologically confirmed biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder or ampulla of Vater cancer); (ii) measurable disease on computed tomography (CT) or magnetic resonance imaging (MRI); (iii) unresectable disease; (iv) no prior chemotherapy; (v) age ≥20 years old; (vi) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (vii) adequate bone marrow function (leukocyte count ≥4000 cells/mm^3, platelet count ≥100 000 cells/mm^3 and hemoglobin ≥9.0 g/dl), renal function (serum creatinine concentration ≤ upper limit of normal) and hepatic function (serum bilirubin level ≤2.0 mg/dl, serum albumin level ≥3.0 g/dl, serum aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 times upper limit of normal); (viii) life expectancy ≥8 weeks; and (ix) written informed consent from the patient. Percutaneous biliary drainage was performed in patients with obstructive jaundice and these patients were required to have serum bilirubin levels of ≤3.0 mg/dl and serum AST and ALT levels ≤5 times the upper limit of normal before enrollment. Exclusion criteria were: serious complications such as active infection, active gastrointestinal ulcer, cardiac disease, or renal disease; central nervous system metastasis; marked pleural effusion or ascites; symptomatic interstitial pneumonitis; and pregnancy or lactation for women. The study was approved by the local institutional review boards at all participating centers.

Treatment Methods

UFT was administered orally at a dose of 300 mg/m^2 per day (400 mg/body per day in patients with body surface <1.50 m^2 and 500 mg/body/day in patients with body surface ≥1.50 m^2) divided into two doses, for 14 consecutive days followed by 1 week of rest. Doxorubicin was given as a 10 min intravenous infusion on Day 1 of each cycle at a dose of 30 mg/m^2. This cycle was repeated every 21 days provided that patients had recovered sufficiently from the drug-related side effects. Patients continued to receive additional courses of this regimen until a maximum of 15 courses, evidence of disease progression or the appearance of unacceptable toxicity. When hematological toxicity greater than grade 3 or non-hematological toxicity greater than grade 2 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). In general, patients were treated as outpatients and admitted to the hospital only for management of toxicities and treatment-related complications.

Assessment of Response and Toxicity

Physical examination, complete blood cell counts, serum chemistries and urinalysis were performed at baseline and at least twice in 3 weeks after initiating treatment. Patients underwent dynamic CT or MRI to evaluate response at 4- to 6-week intervals after the start of treatment. Computed tomography or MRI was performed by obtaining contiguous transverse sections using the helical scanning method at a section thickness of 5 mm. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (18). Objective responses were confirmed by a second evaluation at least 4 weeks later. Toxicity was graded according to the National Cancer Institute common toxicity criteria, version 2.0. Progression-free survival was calculated from the first day of treatment until evidence of tumor progression, clinical progression or death due to any cause. Overall survival was calculated from the first day of treatment until death due to any cause. Survival data were analyzed using the Kaplan–Meier method. The statistical significance of differences between the survival curves was determined using the log-rank test. Differences with P-values <0.05 were considered significant.

Study Designs

The primary end point of this study was the overall response rate, and data from at least 19 patients were accrued. In this study, the threshold response rate was defined as 5% and the expected response rate was set as 15%. If no responses were observed in the 19 patients and the upper limit of the 95%

confidence interval (95% CI) did not exceed the expected rate of 15%, the UFD regimen was judged to have no activity against biliary tract cancer. If response was confirmed in one or more of the 19 patients, the decision of whether or not to proceed to a further study using the UFD regimen was taken on the basis of other factors, such as the safety and rate of response or stable disease in this study.

RESULTS

PATIENT CHARACTERISTICS

A total of 24 patients were enrolled in this study between March 2004 and November 2004. Patient characteristics are shown in Table 1. The 24 patients received 96 cycles of the UFD regimen. The median number of cycles administered per patient was 4 (range, 1–10 cycles). All patients discontinued this treatment: 21 experienced disease progression, two patients refused further treatment because of nausea, vomiting, and/or anorexia and one patient experienced cholangitis. After abandoning the UFD treatment, seven patients received second-line treatment: four patients had systemic chemotherapy with gemcitabine, S-1, UFT or doxorubicin; two patients had radiotherapy; and one patient moved to another hospital to receive immunotherapy. The remaining 16 patients received only the best supportive care after the UFD treatment. The tumor response, toxicity and survival were evaluated on an intention-to-treat basis.

Table 1. Patient characteristics

Variable	No. of patients (n = 24)
Gender	
Male	13
Female	11
Median age (range)	63 (46–75) years
ECOG performance status	
0	16
1	8
Location of primary tumor	
Intrahepatic cholangiocarcinoma	10
Extrahepatic cholangiocarcinoma	1
Gallbladder cancer	13
Extent of disease	
Locally advanced or local recurrence after surgery	5
Metastatic	19
Metastatic sites	
Liver	16
Lymph node	15
Lung	4
Peritoneum	1
Bone	1

ECOG, Eastern Cooperative Oncology Group.

TUMOR RESPONSE

Partial response was achieved in 3 of the 24 patients (2 with intrahepatic cholangiocarcinoma and 1 with gallbladder cancer), but no complete response was observed. Overall response rate was, thus, 12.5% (95% CI 2.7–32.4%). Stable disease was noted in 13 patients (54.2%) and progressive disease (PD) was noted in 7 patients (29.2%). The remaining patient who refused the treatment was not evaluated.

TOXICITY

Toxicities of all 24 patients are shown in Table 2. During treatment, the most common toxicities were nausea and leukopenia, observed in 15 of the 24 patients (62.5%). Other major symptoms were neutropenia, fatigue and anorexia. Grade 3 toxicity was observed in 5 of the 24 patients (20.8%), with anorexia, fatigue, neutropenia and/or anemia. No grade 4 toxicity was observed in any of the 24 patients. There were no treatment-related deaths during the study.

SURVIVAL

Disease progression was finally observed in 23 of the 24 patients, and 18 of the 24 patients died of disease progression. The median progression-free survival was 2.5 months (Fig. 1). The median overall survival time was 7.6 months and the 1-year survival rate was 19.7% (Fig. 2). Figure 3 shows survival curves for patients with intrahepatic or extrahepatic cholangiocarcinoma and for patients with gallbladder carcinoma. The median survival time of the gallbladder carcinoma group was 5.0 months, and that of the intrahepatic

Table 2. Toxicity

Grade	1 (%)	2 (%)	3 (%)	4 (%)
Leukopenia	8 (33.3)	7 (29.2)	0 (–)	0 (–)
Neutropenia	5 (20.8)	8 (33.3)	1 (4.2)	0 (–)
Anemia	7 (29.2)	0 (–)	2 (8.3)	0 (–)
Thrombocytopenia	6 (25.0)	2 (8.3)	0 (–)	0 (–)
Nausea	13 (54.2)	2 (8.3)	0 (–)	0 (–)
Fatigue	12 (50.0)	1 (4.2)	1 (4.2)	0 (–)
Anorexia	7 (29.2)	1 (4.2)	5 (20.8)	0 (–)
Alopecia	7 (29.2)	0 (–)	0 (–)	0 (–)
Vomiting	6 (25.0)	1 (4.2)	0 (–)	0 (–)
Abdominal pain	4 (16.7)	1 (4.2)	0 (–)	0 (–)
Diarrhea	2 (8.3)	0 (–)	0 (–)	0 (–)
Rash	2 (8.3)	0 (–)	0 (–)	0 (–)
Mucositis	1 (4.2)	0 (–)	0 (–)	0 (–)
Taste disturbance	1 (4.2)	0 (–)	0 (–)	0 (–)
Creatinine	1 (4.2)	0 (–)	0 (–)	0 (–)

and extrahepatic cholangiocarcinoma group was 11.0 months. There was a statistically significant difference in the survival curves between the two groups ($P = 0.0034$).

DISCUSSION

No standard chemotherapy for unresectable advanced biliary tract cancer has been established yet. In Japan, only three anticancer agents—UFT, doxorubicin and cytarabine—have been approved for biliary tract cancer by the Ministry of Health, Labor, and Welfare of Japan. Cytarabine is not actually being applied in patients with biliary tract cancer now. Therefore, the practice of systemic chemotherapy in Japan is limited to regimens using UFT and/or doxorubicin. This study was conducted to confirm the efficacy and safety of the combination chemotherapy of UFT and doxorubicin, and the expected response rate was set as 15%. In this study, we achieved a 12.5% response rate, with an additional 54.2% of patients achieving stable disease. The UFD regimen could stabilize biliary tract cancer in 66.7% of the patients treated. Regimens of UFT alone or UFT plus leucovorin were reported to have objective responses of 5 and 0%, respectively, and more than 60% patients were evaluated as having progressive disease in these regimen (15–17). The UFD regimen is considered to have more activity for biliary tract cancer compared with regimens with UFT alone.

With regard to toxicity, the UFD regimen was generally well tolerated. Nausea, fatigue, leukopenia, neutropenia and anorexia were commonly observed but were managed without discontinuing the protocol in most patients. Grade 3 toxicity was observed in 20.8% of patients with anorexia, fatigue, neutropenia, and/or anemia, and no grade 4 toxicity was observed. Considering its safety and convenience, we can use this regimen in outpatient care with only minor toxicity.

In this study, the median overall survival of the UFD regimen was 7.6 months, which was better than 5.2 or 6.5 months of UFT plus leucovorin (15,16). However, the median survival in a study of UFT alone was 8.8 months (17). Recently, gemcitabine has shown promise as a new agent in the treatment of biliary tract cancers. In recent phase II trials, the single agent gemcitabine had an objective response of over 20% (19,20). Moreover, gemcitabine-based combination regimens are reported to have generally higher response rates (21–25). On the other hand, median survivals were also varied in those regimens, from 7.5 to 15.4 months.

Some possible reasons may explain the discrepancy between the response rate and survival in various chemotherapy regimens. Every trial, including the current study, has consisted of a small number of patients, which may be the major cause of the discrepancy. Another reason may be the heterogenicity of biliary tract cancer. The survival can be affected by various factors such as performance status and site of the disease. Chemotherapy favored longer survival in patients with a performance status of 0 or 1, but not in patients with a performance status of 2 (12). Regarding the site of the disease, the median survival in patients with gallbladder cancer was

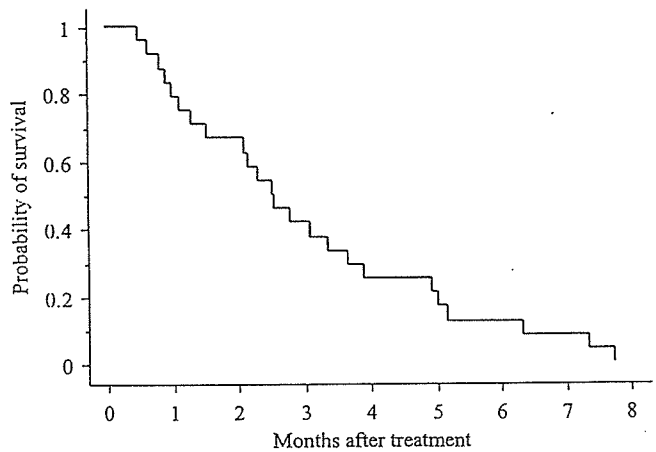

Figure 1. Progression-free survival of all 24 patients. The median progression-free survival was 2.5 months and the 6-month survival rate was 12.5%.

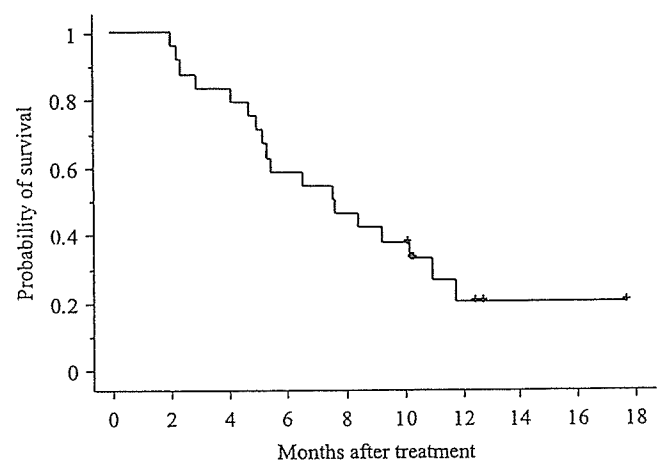

Figure 2. Overall survival of all 24 patients. The median overall survival was 7.6 months, the 6-month survival rate was 58.3%, and the 1-year survival rate was 19.7%.

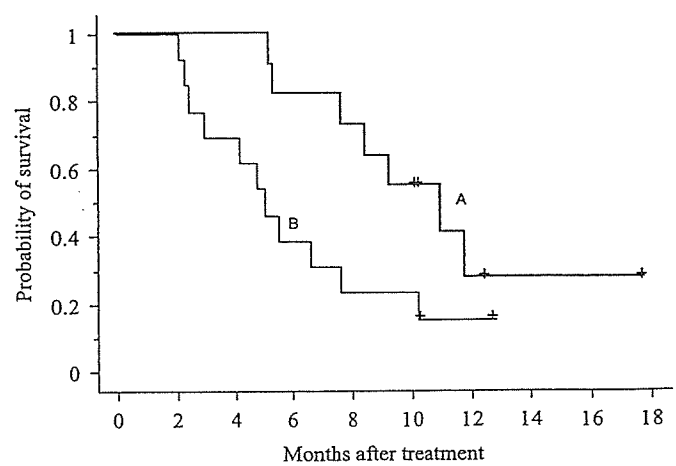

Figure 3. Survival curves of patients with intrahepatic or extrahepatic cholangiocarcinoma (A, $n = 11$) and with gallbladder carcinoma (B, $n = 13$) ($P = 0.034$).

statistically significantly shorter than that in patients with intrahepatic or extrahepatic cholangiocarcinoma in this study. This tendency was seen in another trial of gemcitabine and capecitabine, and it probably reflects the more aggressive biology of gallbladder cancer (24). However, it is not practical to conduct clinical trials separately for gallbladder cancer and cholangiocarcinoma, because each site of these biliary tract cancers is relative rare. In patients with biliary tract cancer, the survival benefit of chemotherapy should be evaluated in randomized studies, including biliary tumor type and performance status in the stratification strategy.

Clinical trials of combination regimen using new anticancer agents, such as gemcitabine, capecitabine and oxaliplatin, have recently been conducted in Western countries (19–24). Whereas clinical trials of a single agent, gemcitabine or S-1, organized by pharmaceutical companies have been conducted in Japan (25,26). This difference between Japan and Western countries is attributable to the system of organizing clinical trials, and in Japan it is almost impossible to conduct clinical trials of new agents not approved by the Ministry of Health, Labor, and Welfare. Biliary tract cancer is rare in Western countries, and large global studies that include Japan should be conducted to establish a standard chemotherapy for biliary tract cancer. A system to conduct or join global clinical trials needs to be established in Japan.

In conclusion, combination chemotherapy with UFT and doxorubicin (the UFD regimen) was well tolerated and showed preliminary moderate activity against advanced biliary tract cancer. Further investigation in late phase II studies in a larger number of patients is recommended, and a multicenter late phase II study is currently ongoing in a Japanese chemotherapy study group for biliary tract and pancreatic cancers.

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EDITORIAL

Serum Tumor Markers for Pancreatic Cancer: The Dawn of New Era?

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Pancreatic cancer accounts for only 3% of all cancers, but it is the fifth leading cause of cancer death in both Western countries [1] and Japan [2]. The prognosis of patients with this disease is extremely poor with less than 5% of patients alive 5 years after diagnosis. Of all the treatment modalities for pancreatic cancer, only resection offers the opportunity for a cure. However, at the time of diagnosis, approximately half of the patients already have metastases and approximately one third of patients are diagnosed as having locally advanced disease, whereas only a small proportion of patients are eligible for surgery. Most symptoms related to this malignancy occur only after disease advancement to an unresectable stages and the early diagnosis of pancreatic cancer remains challenging. To increase the proportion of pancreatic cancer patients with a chance of a cure, there is an urgent need to develop an effective screening system for asymptomatic individuals and to improve the diagnostic accuracy for pancreatic cancer in its early stage. Serum is the most ideal biological specimen for assessing tumor markers in clinical practice because of its availability for repeated collection and reproducible quantification. Recent advancements in technology and an increasing understanding of molecular biology have facilitated research programs into serum markers for pancreatic cancer.

One of the most important roles for serum markers is as a tool for cancer screening in asymptomatic populations. High-quality evidence to justify population-based screening are present for only a few specific malignancies like breast and colorectal cancers but pancreatic cancer has insufficient prevalence in the preclinical population and little availability of adequate modalities for screening. With an estimated prevalence of pancreatic cancer in the population of 0.015%, which is comparable to the latest incidence rate in Japan [3], even a test with sensitivity and specificity of 95% would yield 350 false-positive individuals for every true-positive patient. This example indicates that the screening test needs an almost 100% specificity for this malignancy.

Accuracy in diagnosis for patients with symptoms suspicious of pancreatic cancer is also required for tumor markers in order to distinguish malignancy from benign or non-invasive pancreatic disorders. CA 19-9, the most widely used serum marker for pancreatic cancer diagnosis, had been reported to have a sensitivity of 70-90% and a specificity of 70-98% [4, 5, 6, 7, 8]. Although imaging tests play the main role in the diagnosis of pancreatic cancer, serum markers including CA 19-9 have a considerable predictive value to assist the differential diagnosis in patients with abdominal discomfort or jaundice.

However, currently available serum markers are inadequately sensitive for detection of resectable pancreatic cancer. The Pancreatic Cancer Registry in Japan demonstrated that only 48.4% of the patients with small pancreatic cancer less than 2 cm in diameter had elevated CA 19-9 values [9]. Furthermore, CA19-9 values are considered useless in distinguish neoplasms with high invasive potential, such as mucinous cystic tumors and intraductal papillary mucinous tumors, from those with benign feature [10].

The most commonly accepted uses of serum tumor markers in clinical practice are for assessing the prognosis of, and therapeutic monitoring for pancreatic cancer patients because tumor marker in these situations are more valuable than other modalities including imaging diagnosis. Various studies have demonstrated that CA 19-9 is one of the most significant prognostic factors for both patients with resectable and those with unresectable disease [11, 12, 13, 14, 15]. Measurement of tumor markers as a prognostic factor provides valuable information to assist in the therapeutic decision making especially for surgeons, because early recurrence can be expected in patients with high preoperative levels of the markers. An elevated tumor marker value even after resection indicates the high possibility of remnant disease [16]. The postoperative increase in the value often anticipates the presentation of recurrence in imaging studies or of clinical symptoms. Although the measurement of the tumor size on CT or MR images is standard for evaluation in response to non-surgical treatments such as chemotherapy and radiotherapy, serial change in tumor markers assist the evaluation practically because of the difficulty in accurate measurement of pancreatic mass with obscure margin in most patients, and because of high incidence of the clinically occult progression associated with this disease [17].

Although CA 19-9 is the most useful serum marker for pancreatic cancer, it has some weaknesses. Approximately 10% of the population with the Lewis negative genotype is not able to produce CA 19-9 due to the lack of the enzyme involved in its synthesis, even if they have advanced pancreatic cancer. The Lewis gene dosage positively affects CA 19-9 value, whereas the secretor gene dosage negatively affects it [18]. Patients with small pancreatic cancer often show false negative in the CA 19-9 values. Falsely positive CA 19-9 elevation is frequently observed in patients with benign disease such as chronic pancreatitis. CA 19-9 elevation is common in patients with obstructive jaundice regardless of its malignancy and those with hapatobiliary and gastrointestinal cancer other than pancreatic cancer. Various other serum markers have been developed, although they have not displaced CA 19-9 due to its diagnostic accuracy, especially in the early stage of the disease.

Recent advances in the understanding of the molecular biology of pancreatic cancer facilitate research programs to search for novel markers including tissue-based and circulating markers. Hundreds of over-expressed genes in pancreatic cancer tissues have been identified in investigations using global gene expression. The protein product of an overexpressed gene needs several indispensable characteristics before it can become a sensitive and specific serum-based marker for pancreatic cancer: for example, it should be a secreted protein; it should be overexpressed in pancreatic cancers, it should not be expressed in the nonneoplastic pancreas, and it should have a restricted pattern of expression in other organs and tissues [19]. Several protein products of overexpressed genes including macrophage inhibitory cytokine-1 (MIC-1), synuclein-gamma, mesothelin, and osteopontin have been investigated as potential markers for pancreatic cancer, but their efficacy as serum markers remain undetermined [20, 21, 22]. Detection of aberrantly methylated genes in serum may be a useful diagnostic strategy for pancreatic cancer. The hypermethylation of CpG islands in promoter region is frequently associated with the silencing of tumor-suppressor genes such as p16/CDKN2A, E-cadherin, and others in cancer cells [23, 24]. These abnormalities have been preliminary

reported with promise as tissue- or pancreatic juice-based markers. Hypomethylation of normally methylated genes, which was reported to be identified in serum from patients with testicular cancer, has been recognized in genes including claudin 4, lipocalin 2, 14-3-3 sigma, trefoil factor 2, S100A4, and other, from pancreatic cancer cells or tissues [25, 26, 27, 28].

Proteomics, which is the mass spectrometry-based direct analysis of unknown protein in clinical specimens including serum, has also shown promise in the identification of new biomarkers. Among several technologies for proteomics researches, surface-enhanced laser desorption/ionization (SELDI)-mass spectrometry is considered to be the most useful tools available for the analysis of serum and plasma. A recent study has demonstrated a set of four mass peaks in plasma as most accurately discriminating pancreatic cancer patients from healthy controls in a training cohort with a sensitivity of 97.2% and a specificity of 94.4% and in the validation cohort with a sensitivity of 90.9% and a specificity of 91.1% [29]. The introduction of this technology has enlarged the possibility of identifying novel markers with the potential to overtake and replace CA 19-9.

A bewildering number of investigations to identify useful tumor markers for pancreatic cancer have been conducted, whereas in the vast majority of research studies over the past two decades, CA19-9 alone has been applied as the 'gold standard'. The recent accumulation of knowledge in the molecular biology of pancreatic cancer and rapid advances in technology in this field has enhanced the promising confirmation of novel serum markers with a diagnostic accuracy higher than CA 19-9. The most important obligations for these markers are higher sensitivity to detect early-stage pancreatic cancer and an almost perfect specificity in the screening for this malignancy. The enthusiasm to develop effective molecular targeted agents and other cytotoxic drugs for pancreatic cancer has been increasing rapidly after the introduction of gemcitabine and the recent FDA's approval of erlotinib. These circumstances are also highlighting the need to find the markers in serum and other biological specimens which are able to predict the response to and toxicity of the treatments.

Keywords Biological Markers; CA-19-9 Antigen; Pancreatic Neoplasms

Abbreviations MIC-1: macrophage inhibitory cytokine-1; SELDI: surface-enhanced laser desorption/ionization

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CASE REPORT

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Spontaneous regression of hepatocellular carcinoma

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Abstract We report four patients with hepatocellular carcinoma (all men, with liver cirrhosis and hepatitis C virus infections) who showed spontaneous regression of the tumor. When the spontaneous regression occurred all of the patients were over age 67 years. They showed a rapid increase of serum alpha-fetoprotein levels just before the spontaneous regression of hepatocellular carcinoma. In all the patients, the alpha-fetoprotein level decreased to within normal limits and the tumor was partially to completely reduced in size. One patient revealed regression after bleeding of esophageal varices and blood transfusion. Another showed spontaneous regression after taking several complementary and alternative medicines. However, the mechanisms underlying this intriguing phenomenon remain unknown.

Key words Hepatocellular carcinoma · Spontaneous regression · Hepatitis C virus · Liver cirrhosis

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent human cancers in the world, the incidence being particularly high in South Africa and Asia. The annual international incidence of HCC is more than one million cases diagnosed each year. Most HCC patients have a multiyear history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or alcohol abuse and liver cirrhosis.[1] Most patients are diagnosed at an advanced stage, because of the absence of symptoms in the early stage. The median survival time of patients with HCC is about 6 to 20 months after the onset of symptoms.[2]

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Spontaneous regression (SR) is a rare phenomenon. SR was defined by Everson and Cole[3] as a partial or complete involution of a malignant tumor without a specific therapy being applied. SR of a malignant tumor is estimated to occur in 1 of 60000–100000 cases, almost half involving renal cell carcinoma, neuroblastoma, and malignant melanoma.[4–5] SR of HCC was defined by computed tomography (CT), ultrasonography (US), the serum alpha fetoprotein (AFP) level, or histopathological findings. Although there was no proven specific cause of the regression, we report four HCC patients with SR who had HCV infection and liver cirrhosis.

Case reports

Patient 1

A 70-year-old man was referred to our hospital with a diagnosis of HCC with portal vein tumor thrombosis, in April 1991. He was negative for serological markers of HBV, but antibody to HCV was positive, and he had a history of heavy alcohol intake. He had liver cirrhosis with esophageal varices, and the Child-Pugh score was classified as grade C. Diffuse-type liver tumors in the right lobe were diagnosed as HCC due to typical CT findings and elevation of the AFP level (3360.0 ng/ml). In May 1991, he was admitted to our hospital from the emergency department because of bleeding from esophageal varices; 32 units of packed red blood cells and 44 units of fresh frozen plasma were transfused. In June 1991, CT showed viable tumor volume shrinkage, and the AFP level decreased (19.8 ng/ml) (Fig. 1CD). To obtain a pathological diagnosis, biopsy specimens were obtained, under US guidance, from a shrunken tumor in segment 6. The tumor specimen showed moderately differentiated HCC, Edmonson's II with liver cirrhosis. The HCC regrew in November 1991, and he received multi-disciplinary therapy, including percutaneous ethanol injection (PEI) and transcatheter arterial chemoembolization (TAE). In September 1996, he died due to rupture of the esophageal varices.

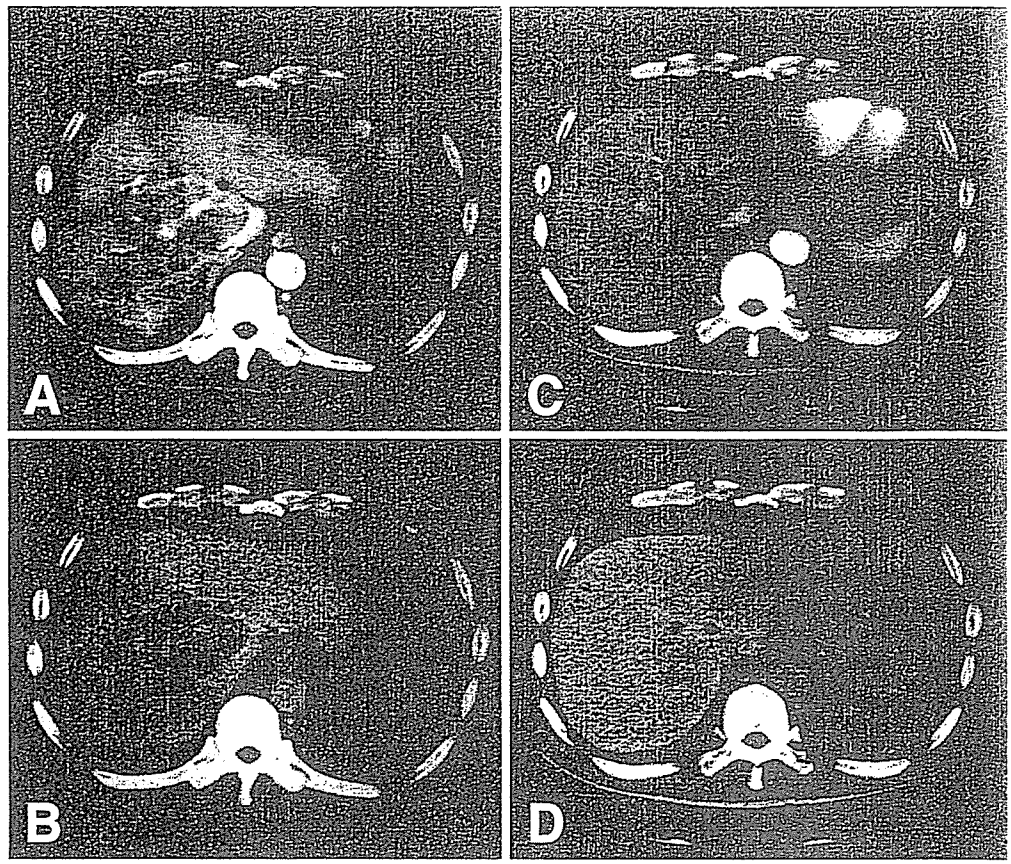

Fig. 1. A, B Computed tomography (CT) scans of patient 1 showed diffuse-type liver tumors located in the right lobe. They had a high density on an early enhanced CT scan in the early phase and a low density on enhanced CT scan in the late phase. **C, D** The right-lobe tumors had decreased markedly in size

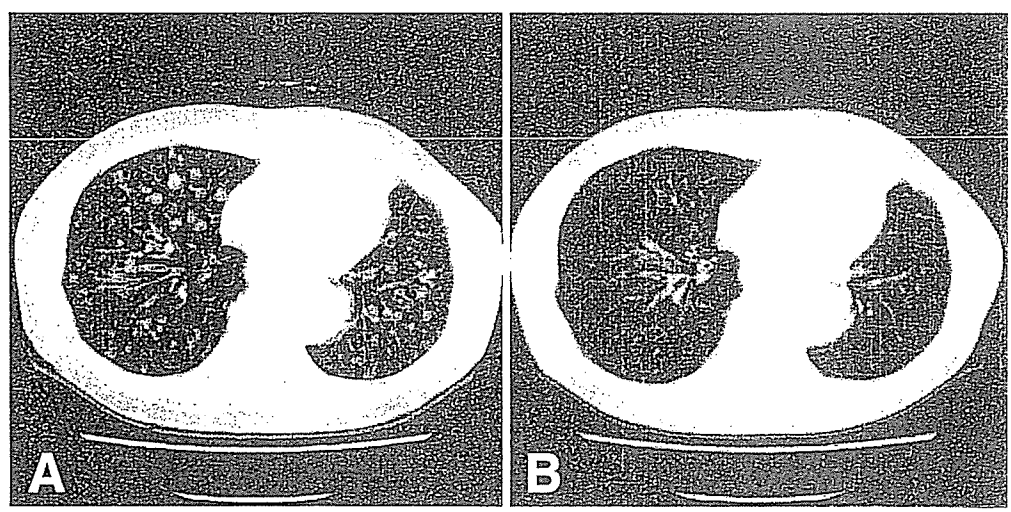

Fig. 2. A CT scan of patient 2 showed multiple nodular lesions scattered in the bilateral lungs, suggesting metastases of hepatocellular carcinoma (HCC). **B** Multiple lung nodules have clearly shrunk

Patient 2

A 75-year-old man was referred to our hospital in February 1995. He was negative for serological markers of HBV, but positive for antibody to HCV. The Child-Pugh score was classified as grade B. Liver tumors were located in segment 7 and diagnosed as HCC by CT, angiographic findings, and an elevated AFP level. He underwent TAE, using gelatin-sponge and Lipiodol combined with zinostatin stimalamer (SMANCS®, Yamanouchi, Tokyo, Japan), in August 1995. Follow-up CT and AFP measurement every 3–4 months did not show any relapse of HCC. In November 1999, he complained of dyspnea and cough. CT revealed multiple nodules in the bilateral lungs, and he had an elevated AFP level (6750.0 ng/ml). The lung nodules were diagnosed as multiple lung metastases of HCC, although the diagnosis was not confirmed pathologically (Fig. 2A). In December 1999, he received systemic chemotherapy using mitoxantrone, cisplatin, and 5-fluorouracil. The efficacy was evaluated as progressive disease with the enlargement of lung nodules and an elevated AFP level (14737.0 ng/ml). Four months after the discontinuation of systemic chemotherapy,

the multiple lung nodules had clearly decreased in number and in size (Fig. 2B). Moreover, the serum AFP level was also reduced (99.3 ng/ml). During this period, he had received neither anticancer treatment nor any medication, including complementary and alternative medicines (CAMs). Furthermore, he had not sustained any infection or trauma. After an 8-month period of spontaneous regression, the residual intrahepatic lesion became larger and the serum AFP level increased again (166.0 ng/ml), although the multiple lung metastatic lesions remained regressed. In September 2000, he underwent TAE, again, for the intrahepatic lesions. In January 2002, he died of liver dysfunction with recurrent HCC.

Patient 3

A 67-year-old man with multiple liver tumors was referred to our hospital in November 2001. He was negative for serological markers of HBV, but antibody to HCV was positive and he had been a social drinker. His Child-Pugh score was classified as grade C. Histological examination showed a poorly differentiated HCC, Edmondson's III, in a segment 4 tumor. Radiofrequency ablation (RFA) was performed in the tumor. No viable lesion in the tumor was identified by CT after the RFA. Follow-up CT examinations did not show any relapse of the HCC. In March 2002, a recurrent tumor with portal vein tumor thrombosis and ascites were detected by CT, and his AFP level increased rapidly (33850.0 ng/ml) (Fig. 3A). He received palliative care from a primary physician, because his general condition was poor and complicated with decompensated cirrhosis and pleural effusion. In July 2003, he was referred to us again because of a decrease in the AFP level noted by the physician. CT showed shrinkage of the primary liver mass and the disappearance of the pleural effusion and ascites (Fig. 3B). The AFP level was within normal limits (7.6 ng/ml). In August 2003, he died of rupture of the esophageal varices, without the recurrence of HCC.

Patient 4

A 67-year-old man was referred to our hospital because of HCC in 1998. He was negative for serological markers of HBV, but antibody to HCV was positive, and he had been a social drinker. The Child-Pugh score was classified as grade B. CT showed a tumor, measuring 3.0 × 3.5 cm, in segment 5, and he had an elevated AFP level (601.0 ng/ml). Biopsy specimens from the tumor showed poorly differentiated HCC, Edmondson's III. In June 1999, PEI was performed in the tumor. In May 2000, RFA was carried out for local recurrent tumor. Recurrent HCC with tumor invading the inferior vena cava was found, and resected in February 2001. CT in July 2001 showed multiple lung metastases and a mass in liver segment 3 and ascites; the AFP level had rapidly increased (89980.0 ng/ml) (Fig. 4A, B). After the findings of multiple metastases, he began to take CAMs. He was transfered to a palliative care unit. Six months later, he was referred to our hospital again, because his performance status had improved and the AFP level had decreased (6.2 ng/ml). The multiple lung nodules and liver tumors had clearly disappeared (Fig. 4C, D). At the time of writing, he was alive without recurrence.

Discussion

Most HCC patients showing SR were men older than 60 years, with underlying chronic liver disease.[6] The mechanism of SR remains unclear. Biological factors that have been suggested in attempts to explain SR include hormonal influences, the withdrawal of agents required for tumor growth, deprivation of oxygen and nutrients, and the activation of immunological variations.[5–7] SR of HCC has also been reported to develop after the withdrawal of androgen,[8] withdrawal of alcohol,[9,10] Taking of herbal medicine,[11–13] blood transfusion,[14] massive bleeding,[14–16] rapid tumor growth,[17,18] fever,[14,19–20] angiography,[21,22] and surgical trauma.[15] All patients in the present report were

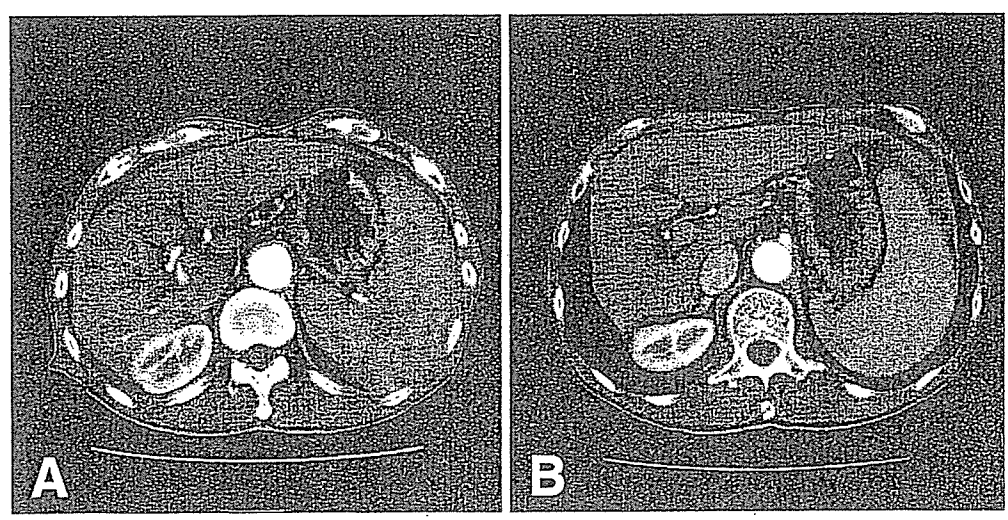

Fig. 3. **A** CT scan of patient 3 showed a tumor in the right lobe, with portal vein tumor thrombosis. **B** Complete spontaneous regression was seen in the right lobe, and the right lobe volume was decreased

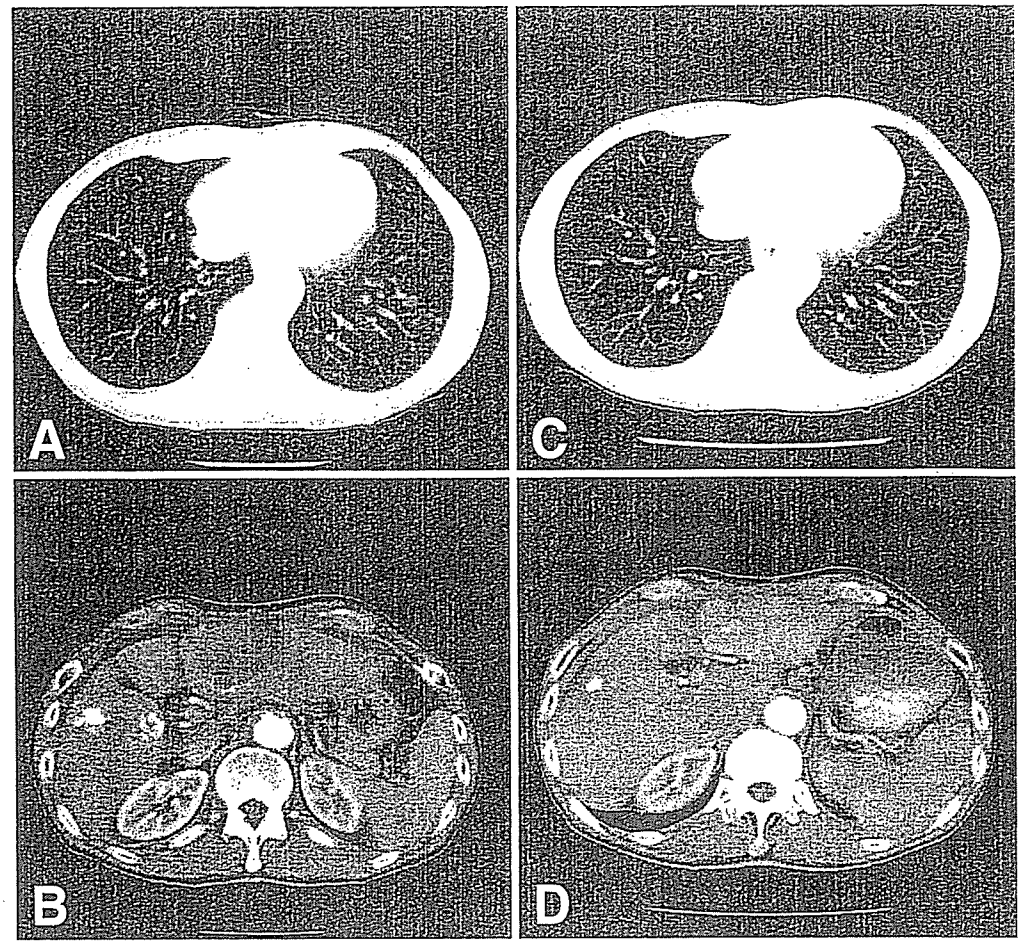

Fig. 4. A, B CT scan of patient 4 in July 2001 showed multiple lung nodules and a liver mass in segment 3. C, D Lung nodules and a liver tumor have disapreared

men, aged 67–75 years, who were positive for HCV antibody, had liver cirrhosis with Child-Pugh grade B or C, showed rapid tumor growth with increasing AFP levels, and had abstained from alcohol after being diagnosed as being HCC-positive. One patient revealed SR after bleeding from esophageal varices and having a blood transfusion. Another patient showed shrinkage of tumor size with the taking of several CAMs. According to previous reports, well- to moderately differentiated HCCs were demonstrated in most patients who showed SR.[9–10,12–14,19,23–24] In our patients who underwent biopsy, the results showed moderately to poorly differentiated HCC. The pathological findings may have no association with SR. We considered the reason for cause of SR in our patients were liver cirrhosis and the rapid growth of HCC.

Cole[5] referred to the possibility that immune systems, which are based on the formation of specific antibodies and immunologically reactive lymphoid cells to antigenic tumor cells, cause SR. Blondon et al.,[25] who reported two cases of SR of HCC, suggested that the dissemination of antigenic tumor cells to the peritoneum induced an antitumor immune response. In another report, the serum levels of cytokines such as interleukin-18 and TNF-alpha were increased at the time of SR.[26] Of the numerous suspected mechanisms of SR, immunological factors may play an important role in this rare phenomenon.[27] These immunological factors are yet to be fully understood, and no studies have been undertaken to investigate them.

The safety and efficacy of many CAMs, including herbal medicines, minerals, vitamins, and substances that increase the total dietary intake, have not been well studied, and rigorous investigations and research into these agents has increased. However the efficacy of CAMs in HCC has been unclear.

The SR of HCC is sporadic, and no precipitating factor has been identified from previous reports or from our cases. The accumulation of such cases of SR will contribute to the further understanding of this intriguing phenomenon and may also lead to a new treatment strategy for HCC.

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ORIGINAL ARTICLE

A phase II study of weekly irinotecan as first-line therapy for patients with metastatic pancreatic cancer

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Abstract
Purpose The aim of this study was to assess the efficacy and toxicity of weekly irinotecan in patients with metastatic pancreatic cancer.
Patients and methods Patients with histologically proven pancreatic adenocarcinoma, at least one bidimensionally measurable metastatic lesion, and no prior chemotherapy were selected. Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. Pharmacokinetics was examined on day 1 of the first cycle of treatment.
Results Thirty-seven of 40 enrolled patients were assessable for efficacy and toxicity. A partial response was obtained in 10 patients, giving an overall response rate of 27.0% (95% confidence interval 13.8–44.1%). The median overall survival was 7.3 months with a 1-year survival rate of 29.5%. Although toxicities were generally tolerated, one patient died of disseminated intravascular coagulation syndrome induced by neutropenia with watery diarrhea. Pharmacokinetic study showed that patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.
Conclusion Single-agent irinotecan has significant efficacy for metastatic pancreatic cancer. The toxicity with this schedule appears manageable, though it must be monitored carefully.

Keywords Irinotecan · Phase II study · Pancreatic cancer · Chemotherapy · Pharmacokinetics

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Introduction

Pancreatic cancer is a highly aggressive disease, with approximately 21,000 deaths annually in Japan [7]. While surgery remains the only potential curative option for this disease, the vast majority of patients unfortunately present with advanced, unresectable disease. Although it has been demonstrated that gemcitabine is

an effective tool for palliation of symptoms and prolonging survival in patients with advanced pancreatic cancer [2], single-agent gemcitabine has shown limited benefit, with objective response rates of less than 15% and a median overall survival of around 4–6 months [2, 4, 5]. Therefore, there is a clear need to identify a new effective chemotherapeutic regimen for pancreatic cancer.

Irinotecan is a water-soluble semisynthetic derivative of camptothecin, a plant alkaloid obtained from the *Camptotheca acuminata* tree. Irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), bind to topoisomerase I (an enzyme required for unwinding of DNA during replication), inducing double-stranded DNA breaks and consequent tumor cell death. Irinotecan is internationally approved for use in metastatic colorectal cancer, and has broad activity against other malignancies including lung cancer [6, 9, 15, 16]. Although several studies of single-agent irinotecan or irinotecan-based chemotherapy against pancreatic cancer have been reported [11, 12, 14, 18, 22], the role of irinotecan in the treatment of patients with pancreatic cancer remains unclear yet. Because there are few effective agents for pancreatic cancer to date, it is important to determine the clinical efficacy of irinotecan for this disease. We, therefore, conducted an open-label, multicenter, single-arm phase II study to evaluate the efficacy and toxicity of single-agent irinotecan in patients with pancreatic cancer. In the current study, we adopted weekly administration of irinotecan because safety of this schedule has been confirmed in other cancers in Japan [6, 9, 16]. Since patients with pancreatic cancer tend to suffer various tumor-related complications such as obstructive jaundice and impaired liver function, pharmacokinetic study was also performed.

Patients and methods

Patient selection

Patients were entered into the study if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma of the pancreas; at least one bidimensionally measurable metastatic lesion; no history of prior chemotherapy or radiotherapy; age 20–74 years; Karnofsky performance status (KPS) ≥ 50 points; estimated life expectancy ≥ 2 months; adequate bone marrow function (WBC count $< 12{,}000$ per mm^3, neutrophil count $\geq 2{,}000$ per mm^3, platelet count $\geq 100{,}000$ per mm^3, and hemoglobin level ≥ 10.0 g/dl), adequate renal function (serum creatinine and blood urea nitrogen level $\leq$ the institutional upper limit of normal), and adequate liver function (serum total bilirubin level ≤ 2.0 mg/dl, serum transaminases levels ≤ 2.5 times the institutional upper limit of normal); and written informed consent. Patients were excluded if there was a history of severe drug hypersensitivity; serious complications; central nervous system metastases; other concomitant malignant disease; marked pleural or peritoneal effusion; and watery diarrhea. Pregnant or lactating women were also excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the institutional review board of each participating center, and conducted in accordance with Good clinical practice guideline in Japan.

Treatment plan

This study was an open-label, multicenter, single-arm phase II study. Irinotecan was supplied by Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) and Yakult Honsha Co., Ltd. (Tokyo, Japan). Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal to continue. Prophylactic administration of antiemetic agents was allowed at the investigator's discretion. Physical examination, complete blood cell counts, biochemistry tests, and urinalysis were assessed weekly during treatments. If patients experienced neutropenia of $< 1{,}500$ per mm^3, thrombocytopenia of $< 100{,}000$ per mm^3, fever ($\geq 38°C$) with suspected infection, grade ≥ 1 or watery diarrhea, or $\geq$ grade 3 non-hematological toxicities other than nausea, vomiting and anorexia, irinotecan administration was omitted on that day and postponed to the next scheduled treatment day. If patients experienced neutropenia of < 500 per mm^3, thrombocytopenia of $< 50{,}000$ per mm^3, fever ($\geq 38°C$) with suspected infection, or grade ≥ 2 or watery diarrhea at any time, the irinotecan dose of the subsequent cycle was reduced by 20 mg/m^2. Patients went off study if they required more than two dose reductions. If the next cycle could not start within 4 weeks from the scheduled day, the patient was withdrawn from the study. The toxicity of irinotecan therapy was evaluated according to the National Cancer Institute Common Toxicity criteria version 2.0.

Evaluation

Objective tumor response was evaluated every 4 weeks according to the Japan Society for Cancer Therapy (JSCT) criteria [8], which is similar to the WHO crite-

ria. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks. A partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. No change (NC) was defined as a $< 50\%$ reduction or a $< 25\%$ increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. Progressive disease (PD) was defined as a $\geq 25\%$ increase or the appearance of new lesions. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately [1]. Objective tumor response was secondarily assessed according to the response evaluation criteria in solid tumors (RECIST criteria) [20] among patients with at least one measurable metastatic lesion whose longest diameter measured by CT is no less than double the slice thickness. An external review committee confirmed objective responses and toxicities.

Clinical benefit was evaluated on the basis of established criteria [13]. Each patient was classified as a clinical benefit responder or non-responder on the basis of the change in two parameters of clinical benefit (pain and KPS). In the current study, the body weight was not used to evaluate clinical benefit response because the body weight of patients with pancreatic cancer sometimes increases due to not only improvement of their condition but also retention of malignant ascites. A positive response for pain was defined as an improved pain intensity of $\geq 50\%$ from baseline for ≥ 4 weeks, or a decreased morphine consumption of $\geq 50\%$ from baseline for ≥ 4 weeks. A positive response for KPS was defined as an improved KPS of ≥ 20 points from baseline for ≥ 4 weeks. To be classified as a clinical benefit responder, a patient had to achieve a positive response in at least one parameter (pain or KPS) without being negative for the other, sustained for ≥ 4 weeks.

Pharmacokinetics

To investigate the impact of biliary drainage on pharmacokinetics of irinotecan, we planned to recruit five patients each with and without biliary drainage. Heparinized blood samples (5 ml) for the pharmacokinetic study were obtained before infusion of irinotecan, at the end of the 90 min infusion, and 0.5, 1, 2, 4, 6, 8, 24 h after the completion of infusion on day 1 of the first cycle. Blood samples were immediately centrifuged at 3,000 rpm for 10 min to remove plasma and stored in polyethylene tubes at −20°C until analysis. Quantitative analysis of total irinotecan and its metabolites, SN-38, SN-38 glucuronide, and 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) was performed by methods previously described [17, 19].

Statistical analysis

The primary goal was to evaluate the response rate (CR and PR) of irinotecan. The 95% confidence interval for response rate was calculated based on the binomial distribution. The response duration was defined as the interval from the first documentation of response to the first documentation of tumor progression. The time to progression (TTP) was calculated from the date of study enrollment to the first documentation of tumor progression; and overall survival was calculated from the date of study enrollment to the date of death or the last follow-up with censored value. Median overall survival and the median TTP were estimated by the Kaplan–Meier method and 95% confidence interval were estimated based on the Greenwood's formula. A total of 35 patients were planned to be enrolled based on the assumptions that the expected response rate of irinotecan was 15% and the threshold rate was 5%. A two-stage design was used in this study. The interim analysis was planned when 15 patients were enrolled in the first stage of the study. If the upper limit of the 90% confidence interval (one-sided) did not exceed the expected rate of 15% (no objective response in the 15 patients), irinotecan was judged to be ineffective and the study was ended. If an objective response was observed in any of the first 15 patients, additional 20 patients were enrolled in the second stage of accrual to estimate the response rate. If 6 or more out of 35 patients achieved objective response, the lower limit of the 95% confidence interval (two-sided) exceeds the threshold rate of 5%, and then the agent would be considered to be active for metastatic pancreatic cancer.

Results

Patients

Forty patients were enrolled in the study by 7 institutions between August 2001 and November 2002. Of the 40 patients, 3 patients who did not receive irinotecan because of rapid tumor progression or protocol violation were excluded from analysis. Patient characteristics of the remaining 37 patients are listed in Table 1.

All 37 patients had metastatic disease and had a good KPS of ≥ 80. Morphine was prescribed for 10 patients due to abdominal or back pain and 14 patients were assessable for clinical benefit response. Seven patients had recurrent disease after pancreatic resection. Two patients underwent percutaneous transhepatic biliary drainage for obstructive jaundice prior to study enrollment.

Treatments

Data were collected through May 4, 2004, providing 18 months of survival follow-up from the time accrual ended. Thirty-seven patients were given a total of 108 cycles of therapy, with a median of 2 cycles each (range 1–10). The administration of irinotecan on day 8 and day 15 was performed in 87 (80.6%) and 76 (70.4%) of 108 cycles, respectively. Dose reduction was required in 13 patients (35.1%), mainly due to diarrhea and fever with suspected infection. At the time of analysis, all patients had discontinued the study because of disease progression ($n = 28$), toxicity ($n = 5$), treatment-related death ($n = 1$), and withdrawal of consent due to other reasons ($n = 3$). After discontinuation of irinotecan, 26 patients received gemcitabine monotherapy or gemcitabine-based combination therapy; one patient was treated with S-1, and remaining 10 patients underwent only supportive care. Among 27 patients treated with second-line chemotherapy, 2 patients who received gemcitabine monotherapy achieved a PR.

Table 1 Patient characteristics ($n = 37$)

Characteristics		No. of patients (%)
Gender		
Male		25 (67.6)
Female		12 (32.4)
Median age, years (range)	59 (41–74)	
Karnofsky performance status, point		
100		8 (21.6)
90		25 (67.6)
80		4 (10.8)
Median body surface area (m^2) (range)	1.55 (1.31–1.85)	
History of surgical resection		7 (18.9)
PTBD		2 (5.4)
Sites of metastasis		
Liver		33 (89.2)
Lymph nodes		17 (45.9)
Lung		8 (21.6)
Others		3 (8.1)

PTBD percutaneous transhepatic biliary drainage

Efficacy

Of 37 patients, 10 patients achieved a PR according to the JSCT criteria (Table 2). The overall response rate was therefore 27.0% (95% confidence interval 13.8–44.1%) with median response duration of 4.1 months (range 0.9–7.1 months). The median TTP was 2.1 months (range 0.7–9.5 months), and the median overall survival of 7.3 months (range 0.7–25.9 months) with a 1-year survival rate of 29.5% (Fig. 1). Of 29 patients assessable for RECIST criteria, a PR was seen in 8 patients (27.6%), stable disease in 6 patients (20.7%), and PD in 12 patients (41.4%). With regard to clinical benefit, 2 of 14 evaluable patients had pain relief and were classified as a responder (Table 3).

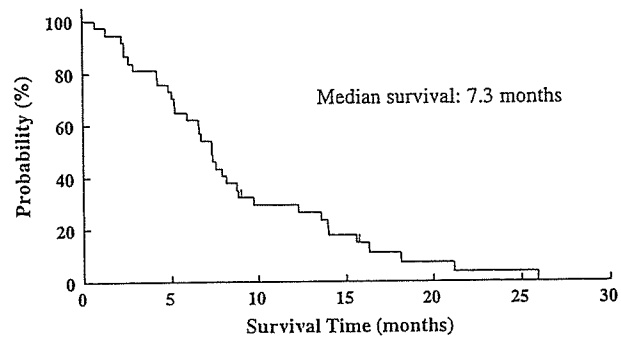

Fig. 1 Overall survival curve of all 37 patients

Table 2 Efficacy results

	No. ($N = 37$)	%
Tumor response		
Partial response	10	27.0
No change	7	18.9
Progressive disease	17	45.9
Not evaluable	3	8.1
Time to progression (months)		
Median	2.1	
Range	0.7–9.5	
Overall survival (months)		
Median	7.3	
Range	0.7–25.9	
1-year survival rate		29.5

Table 3 Clinical benefit response ($n = 14$)

		Karnofsky performance status		
		Improved	Stable	Worse
Pain	Improved	0	2	0
	Stable	0	6	1
	Worse	0	5	0

Toxicity

All 37 patients were assessable for toxicity. The major toxicities observed during the study are summarized in Table 4. The most common toxicities were hematological toxicity and gastrointestinal toxicity. Grade 3 or 4 neutropenia occurred in 10 patients (27.0%) and 5 patients received granulocyte-colony stimulating factors. The neutrophil count nadir typically occurred on day 21, and recovered to baseline values by day 28. Although nausea, vomiting, and anorexia were observed frequently, most of these toxicities recovered spontaneously or with adequate supportive treatment. Grade 3 diarrhea occurred in four patients and they were treated with loperamide. Most diarrheas appeared during the first cycle of treatment: the median time to the worst day of diarrhea was 13 days from the initiation of a cycle of therapy. Though the toxicities were mild to moderate in severity and short in duration, one patient died at day 21 of the first cycle of treatment because of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and watery diarrhea due to irinotecan. The patient, a 58-year old woman with pretreatment KPS of 100, developed grade 4 neutropenia on day 12 complicated by fever (38.8°C) and grade 3 diarrhea that evolved to fatal shock despite aggressive medical management.

Table 4 Treatment-related adverse events ($n = 37$): worst grade reported during treatment period

Toxicity	Grade				Grade 1–4 (%)	Grade 3–4 (%)
	1	2	3	4		
Hematologic						
Leukopenia	15	6	8	1	81.1	24.3
Neutropenia	5	11	8	2	70.3	27.0
Anemia	0	14	3	0	45.9	8.1
Thrombocytopenia	1	1	1	1	10.8	5.4
Non-hematologic						
Nausea	7	12	15	–	91.9	40.5
Vomiting	7	14	5	0	70.3	13.5
Diarrhea	15	8	4	0	73.0	10.8
Constipation	1	8	2	0	29.7	5.4
Anorexia	4	7	14	1	70.3	40.5
Stomatitis	2	0	0	0	5.4	0
Rash	1	0	0	0	2.7	0
Alopecia	24	1	–	–	67.6	–
Fatigue	3	8	1	1	35.1	5.4
Fever	3	1	0	0	10.8	0
Infection	2	1	4	1	21.6	13.5
Total bilirubin	4	1	1	0	16.2	2.7
AST	5	5	2	0	32.4	5.4
ALT	4	4	3	0	29.7	8.1
Hyponatremia	6	0	3	0	24.3	8.1
Creatinine	0	0	2	0	5.4	5.4

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Pharmacokinetics

A pharmacokinetic analysis was performed in five patients without biliary drainage and in two patients who underwent percutaneous transhepatic biliary drainage (Planned five patients could not be enrolled in drainage group because only two patients had biliary drainage in the current study). Table 5 and Fig. 2 show the pharmacokinetic parameters for irinotecan and its three major metabolites in patients with and without biliary drainage. Although it was difficult to assess the influence of biliary drainage in this study because of the small number of subjects analyzed, patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.

Discussion

The prognosis of the patients with pancreatic cancer remains poor even after a randomized study demonstrated survival advantage of gemcitabine against advanced pancreatic cancer, indicating necessity of new effective agents or combination regimens for this dismal disease. Irinotecan, which has a quite different mechanism from gemcitabine, has been considered one of the attractive agents for pancreatic cancer, since this agent has demonstrated substantial activity in various types of malignant tumor [6, 9, 15, 16]. The current multicenter phase II study was, therefore, conducted to evaluate the efficacy and toxicity of single-agent irinotecan in patients with metastatic pancreatic cancer.

In this study, we found that weekly irinotecan demonstrated a good overall response rate of 27.0% in 37 patients with metastatic pancreatic cancer. In addition, a relatively long median overall survival of 7.3 months was shown, though all patients in our study had metastatic disease. As to clinical benefit response, 2 of 14 patients achieved clinical benefit response. These results indicate that irinotecan has a substantial antitumor effect on pancreatic cancer.

The major toxicities of irinotecan that were seen in the study were myelosuppression and gastrointestinal toxicities, similar to the previous observation of irinotecan monotherapy in other cancers [6, 9, 16]. Most toxicity was mild to moderate, and manageable with conservative treatment. However, one patient died of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and diarrhea. Pretreatment condition of this patient was good (KPS = 100), and it was difficult to predict these