The proportion of AIDS cases whose risk was not reported was extremely high in Japan. This is due to the fact that, in Japan, the physician in charge investigates the route of infection only at the time of diagnosis, and further inquiries are not conducted. For HIV-infected cases, the proportions were also substantially high in other countries. However, it should be noted that, in all countries, except Japan, this exposure category included cases that were currently being followed up by local health department officials. Individuals whose routes of infection are identified in the follow-up will be reclassified into the appropriate exposure categories.

Increasing trends at the onset of the epidemic

The increasing trend in Japan at the onset of the epidemic was extremely slow compared to other industrialized countries. This was due to the fact that, in Japan, there were few cases infected through MSM and/or IDU. The increasing trend in the number of cases infected through heterosexual contact was also relatively slow in Japan. The reason for this seems to be that in Japan those who tested positive were older as shown in Table 3. It is assumed that the sexual activity of such individuals is lower than that of individuals in their 20's and 30's. Information regarding heterosexual contact according to the exposure risk of partners was obtained from the UK surveillance[16]. Figure 4[16] shows the trends for the number of women infected through heterosexual contact. At the onset of the epidemic, there were more cases with partners at high risk such as IDU and MSM, and the cases whose partners were not at high risk began to increase thereafter. This result suggests that, in Japan, it might be necessary to examine trends in the number of reported cases through heterosexual contact according to the risk of partners. Such analysis will be possible if such information is added to the current surveillance report forms in the future.

Acknowledgements

This study was supported by a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Japan, for Research on HIV/AIDS.

Reference

1) Centers for Disease Control and Prevention HIV/AIDS Surveillance Report, 13 (No 2) : 1-44, 2001.
2) European Centre for the Epidemiological Monitoring of AIDS : HIV/AIDS Surveillance in Europe. End-year report 2001, Saint-Maurice : Institut de Veille Sanitaire, No 66 : 2002.
3) Health Canada : HIV and AIDS in Canada. Surveillance Report to December 31, 2001. Division of HIV/AIDS Epidemiology and Surveillance, Centre for Infectious Disease Prevention and Control, Health Canada, 2002.
4) National Centre in HIV Epidemiology and Clinical Research : HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2002. National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW, 2002.
5) AIDS Surveillance Committee, Ministry of Health, Labor and Welfare, Japan : Annual Surveillance Report of HIV/AIDS in Japan, 2002. (in Japanese)
6) Hashimoto S, Fukutomi K, Morio S, Ishikawa S, Yamamoto N, Naemura M, Soda K : Prediction of future trends of HIV infection and AIDS in Japan. Jpn J Public Health 40 : 926-933, 1993. (in Japanese)
7) Hashimoto S, Fukutomi K, Morio S, Ishikawa S, Yamamoto N, Naemura M, Soda K : The trend in the number of HIV-infected persons and AIDS cases based on the HIV/AIDS surveillance data in Japan. Jpn J Public Health 40 : 1184-1195, 1993. (in Japanese)
8) Kihara M, Ichikawa S, Soda K, Kihara M, Hashimoto S, Shinmura K : Analysis of cause of recent rise in number of foreigners reported to HIV/AIDS surveillance in Japan. Jpn J Public Health 42 : 569-578, 1995. (in Japanese)
9) Hashimoto S, Fukutomi K, Ichikawa S, Morio S, Shinmura K, Soda K : Some problems on the estimation of the numbers of HIV-infected persons and AIDS cases based on AIDS surveillance data. Jpn J Public Health 42 : 1091-1098, 1995. (in Japanese)
10) Kihara M, Ichikawa S, Kihara M, Yamasaki S : Descriptive epidemiology of HIV/AIDS in Japan, 1985-1994. J Acquir Immune Defic Syndr Hum Retrovirol 14 (suppl 2) : S3-S12, 1997.
11) Matsuyama Y, Hashimoto S, Ichikawa S, Nakamura Y, Kidokoro T, Umeda T, Kamakura M, Kimura S, Fukutomi K, Ikeda C, Kihara M : Trends in HIV and AIDS based on HIV/AIDS surveillance data in Japan. Int J Epidemiol 28 : 1149-1155, 1999.
12) Matsuyama Y, Hashimoto S, Ichikawa S, Nakamura Y, Kidokoro T, Fukutomi K, Kihara M : Trends in the number of death cases reported to the HIV/AIDS surveillance. J AIDS Res 2 : 30-34, 2000. (in Japanese)
13) Hashimoto S, Fukutomi K, Ichikawa S, Matsuyama Y,

Nakamura Y, Kihara M : Future prediction of the number of HIV-infected persons and AIDS cases. J AIDS Res 2 : 35-42, 2000. (in Japanese)

14) Umeda T, Kihara M, Hashimoto S, Ichikawa S, Kamakura M, Shimamoto T : Characteristics of AIDS cases infected through heterosexual contact in Japan. Jpn J Public Health 48 : 200-207, 2001. (in Japanese)

15) Umeda T : HIV/AIDS situation in Japan. J Epidemiol 6 : S133-S137, 1996.

16) Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre, ICH (London), SCIEH. HIV & AIDS in the United Kingdom 2001 : London, An update November, 2002.

17) Robert Koch Institut. Epidemiologisches Bulletin : HIV/AIDS-Bericht II/2001.

18) AIDS Operational Centre (COA) of the Institute : Newsletter of the Italian National Institute of Health : Updating of notified cases of AIDS in Italy, No 15 (3) : 2002. (in Italian)

19) National Center of Epidemiology : HIV and AIDS in Spain, No 1 : 2002. (in Spanish)

20) Institut de Veille Sanitaire : Bulletin epidemiologique hebdomadaire, Surveillance du SIDA en France. No 27 : 2002.

21) UNAIDS/WHO : Global HIV/AIDS and STD Surveillance : Epidemiological facts sheets by country, 2002 update.

22) Hashimoto S, Matsumoto T, Nagai M, Matsuyama Y, Nakamura Y, Umeda T, Kamakura M, Ichikawa S, Kimura S, Fukutomi K, Kihara M : Delays and continuation of hospital visits among HIV-infected persons and AIDS cases in Japan. J Epidemiol 10 : 65-70, 2000.

British Journal of Cancer (2004) 91, 673–677

www.bjcancer.com

Phase II study of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer

T Okusaka*[,1], Y Ito[2], H Ueno[1], M Ikeda[1], Y Takezako[1], C Morizane[1] Y Kagami[2] and H Ikeda[2]

[1]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; [2]Radiation Oncology Division, National Cancer Center Hospital, Tokyo, Japan

Gemcitabine has been reported to be a potent radiosensitiser in human pancreatic cell lines. This study was conducted to evaluate the efficacy and toxicity of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer. In all, 42 patients with pancreatic cancer that was unresectable but confined to the pancreatic region were treated with external-beam radiation (50.4 Gy in 28 fractions over 5.5 weeks) and weekly gemcitabine (250 mg m^{-2}, 30-min infusion). Maintenance gemcitabine (1000 mg m^{-2} weekly × 3 every 4 weeks) was initiated 1 month after the completion of the chemoradiotherapy and continued until disease progression or unacceptable toxicity. Of the 42 patients, 38 (90%) completed the scheduled course of chemoradiotherapy. The major toxicity was leucopenia and anorexia. There was one death attributed to duodenal bleeding and sepsis. The median survival time was 9.5 months and the 1-year survival rate was 28%. The median progression-free survival time was 4.4 months. In 35 patients with documented disease progression at the time of analysis, 34 (97%) showed distant metastasis as the cause of the initial disease progression. The chemoradiotherapy used in this study has a moderate activity against locally advanced pancreatic cancer and an acceptable toxicity profile. Future investigations for treatment with more systemic effects are warranted.
British Journal of Cancer (2004) **91**, 673–677. doi:10.1038/sj.bjc.6602001 www.bjcancer.com
Published online 29 June 2004

Keywords: pancreatic cancer; chemoradiotherapy; gemcitabine; radiosentitiser

Pancreatic cancer is the fourth leading cause of cancer death in the United States and the fifth leading cause in Japan. The statistics indicate a rapid increase in the number of deaths and the death rate due to pancreatic cancer in Japan, but the precise reasons are not clear, except for smoking. Pancreatic cancer in most patients is surgically unresectable at the time of diagnosis because of the difficulty of early detection of this disease. For patients with locally advanced pancreatic cancer, chemoradiotherapy has been accepted as standard treatment because the results of previous randomised trials have indicated that concurrent external-beam radiation therapy and 5-fluorouracil (5-FU) therapy results in a significantly longer survival time than radiotherapy (Moertel *et al*, 1969; Gastrointestinal Tumor Study Group, 1981) or chemotherapy alone (Gastrointestinal Tumor Study Group, 1988). In attempts to improve the efficacy of the treatment, numerous trials using modified approaches of chemoradiotherapy have been conducted (Chakravarthy and Abrams, 1997; Okada, 1999). However, there has not yet been a regimen that has demonstrated superiority over conventional chemoradiotherapy performed in randomised controlled trials.

Gemcitabine is a novel deoxycytidine analog, which has demonstrated significant clinical benefit and survival improvement compared with 5-FU in patients with advanced pancreatic cancer (Burris *et al*, 1997). Gemcitabine has also been shown to be a potent radiosensitiser in human pancreatic and other solid tumour cell lines (Lawrence *et al*, 1996; Shewach and Lawrence, 1996; van Putten *et al*, 2001), suggesting that the combination of radiotherapy and gemcitabine may improve survival in patients with locally advanced disease. A phase I trial that was conducted in our hospital determined the recommended dose of weekly gemcitabine for the phase II chemoradiotherapy trial to be 250 mg m^{-2} (Ikeda *et al*, 2002). We report our results of the phase II study that was conducted to clarify the efficacy and toxicity of concomitant chemoradiotherapy with gemcitabine in patients with locally advanced pancreatic cancer.

*Correspondence: Dr T Okusaka; E-mail: tokusaka@ncc.go.jp
Received 29 March 2004; accepted 24 May 2004; published online 29 June 2004

PATIENTS AND METHODS

Patients eligible for this study had locally advanced pancreatic cancer for which they had not received any anticancer treatment. Each patient was required to meet the following eligibility criteria: pathological proof of adenocarcinoma of the pancreas; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate bone marrow reserve (white blood cell count $\geqslant 4000\,mm^3$, platelet count $\geqslant 100\,000\,mm^3$, haemoglobin level $\geqslant 10\,g\,dl^{-1}$); adequate renal function (normal serum creatinine and blood urea nitrogen levels, and a creatinine clearance level $\geqslant 60\,mg\,min^{-1}$); a serum aspartate aminotransferase (AST) level <2.5 times upper normal limit (UNL); a serum alanine aminotransferase (ALT) level <2.5 times UNL; and written informed consent. Patients with obstructive jaundice were

required to have a serum total bilirubin level of less than 2.0 mg dl^{-1} after biliary drainage. Pretreatment staging included ultrasonography and dynamic computed tomography (CT) scans of both the abdomen and the chest. The possibility for resection of the local tumour was assessed by dynamic CT and/or angiography. Obstruction or bilateral invasion of the portal vein and/or tumour encasement of the celiac or superior mesenteric arteries was considered to be unresectable. Patients were excluded if they met the following criteria: concomitant malignancy, pleural and/or peritoneal effusion, active ulcer of the gastrointestinal tract, active infection, severe heart disease, pregnant or lactating females, or other serious medical conditions. The goal was set at 40 eligible patients. This number of patients was planned using a design based on the assumptions that the median survival time in conventional chemoradiotherapy was 10 months, expected median survival time was 14 months, type I error was 5% (one-tailed) and statistical power was 70%.

Radiotherapy was delivered via a racetrack microtron (MM50, Scanditronix, Upsala, Sweden) with a 25 MV X-rays. A total dose of 50.4 Gy was delivered in 28 fractions over 5.5 weeks. All patients had treatment planning, CT scans (X-vision, Toshiba, Tokyo) and FOCUS (version 3.2.1, CMS, St Louis, MO, USA) was used as a radiotherapy treatment planning system. Clinical target volume (CTV) included the primary tumour, nodal involvement detected by CT scan and regional draining and paraaortic lymph nodes, which included the peripancreatic nodes, celiac and superior mesenteric axes. Planning target volume was defined as CTV plus a 10-mm margin. Four field techniques (anterior, posterior and opposed lateral fields) were used. Spinal cord dose was maintained below 45 Gy and $\geqslant$50% of liver was limited to $\leqslant$30 Gy, $\geqslant$50% of both kidneys were limited to $\leqslant$20 Gy.

Gemcitabine at a dose of 250 mg m^{-2} was given intravenously over 30 min starting 2 h before radiotherapy weekly for 6 weeks. This schedule was based on an *in vitro* study which revealed that gemcitabine induced its radiosensitising effect in cells within 2 h (Lawrence *et al*, 1997). Toxicity was assessed according to the National Cancer Institute - Common Toxicity Criteria version 2.0. When grade 3 haematological toxicity, serum creatinine of 1.5–2.0 times UNL, total bilirubin level of 3.0–5.0 times UNL, serum AST/APT of 5.0–10 times UNL and/or grade 2 nonhaematological toxicity (excluding nausea, vomiting, anorexia, fatigue, constipation, alopecia and dehydration) were observed, gemcitabine administration was omitted and postponed to the next scheduled treatment day. The radiotherapy was also suspended, and then resumed when the toxicities recovered. In patients who experienced the above adverse effects, dose reduction of gemcitabine to 200 mg m^{-2} was allowed in subsequent administrations. The combined treatment was discontinued when grade 3 leucopenia and/or neutropenia with high fever, grade 4 haematological toxicities after dose reduction of gemcitabine, serum creatinine of $>$2.0 times UNL, total bilirubin level of $>$5.0 times UNL, serum AST/APT of $>$10 times UNL, grade 3 or 4 nonhaematological toxicities (excluding nausea, vomiting, anorexia, fatigue, constipation, alopecia and dehydration), grade 4 vomiting, a total of 2 weeks of delay due to toxicity for any reason or tumour progression were observed. At 1 month after the completion of chemoradiotherapy, maintenance chemotherapy of gemcitabine at a dose of 1000 mg m^{-2} was administered as a 30-min intravenous infusion weekly for 3 weeks with 1-week rest until disease progression or unacceptable toxicity. Follow-up CT was performed within 1 week after the completion of chemoradiotherapy, and thereafter every 2 months to evaluate tumour response according to the WHO criteria (World Health Organization, 1979).

Progression-free and overall survival times were calculated from the first day of treatment using the Kaplan–Meier method (Kaplan and Meier, 1958). Serum CA 19-9 levels were measured monthly by a radioimmunometric assay using the Centocor radioimmunoassay kit (Centocor, Inc., Malvern, PA, USA).

RESULTS

Patients and treatments

In all, 42 patients were enrolled in the study between July 2001 and July 2002. Patient characteristics are listed in Table 1. A total of 38 patients (90%) received the full regimen of chemoradiotherapy, and the remaining four patients (10%) discontinued the treatment after 18.0–45.0 Gy. The reasons for the treatment discontinuation were elevated serum ALT of $>$10 times UNL (two patients), duodenal bleeding (one), and patient's refusal of treatment due to general fatigue (one). After discontinuation of the chemoradiotherapy, the two patients who showed the ALT elevation suspected as gemcitabine-related toxicity received chemoradiotherapy using 5-FU, and the other two patients underwent only supportive care. Of 241, 30 (12%) planned gemcitabine injections (0.7 injections per patient) were omitted owing to adverse events including grade 3 or more leucopenia and/or neutropenia, grade 2 fever, grade 2 skin rash and patient's refusal due to nausea, vomiting or fatigue. In three patients who showed grade 4 leucopenia and/or neutropenia, the dose of gemcitabine was modified in subsequent injections. Maintenance chemotherapy was initiated in 23 of the 38 patients who completed the full regimen of chemoradiotherapy. Of the remaining 15 patients, seven showed deterioration of general condition due to disease progression before initiating the chemotherapy, seven refused the treatment due to appetite loss (4) or general fatigue (3) and one transferred to another hospital (1).

Response and survival

Tumour response was determined in 40 patients. Two patients were excluded from the protocol efficacy analysis because their treatment was switched over to chemoradiotherapy using 5-FU before the response evaluation due to the ALT elevation. Nine patients (21%) achieved a partial response, 26 (62%) remained stable and five (12%) showed progressive disease demonstrated by the development of distant metastases. No patients could undergo tumour resection even after the completion of chemoradiotherapy because of infiltration of the adjacent large vessels. In 22 (76%) of the 29 patients with a pretreatment serum CA19-9 (carbohydrate antigen 19-9) level of 100 U ml^{-1} or greater, the level was reduced more than 50% within 14 weeks after initiation of treatment.

Table 1 Patient characteristics

Number of patients	42
Gender	
Male	19 (45%)
Female	23 (55%)
Age (years)	
Median (range)	59 (43–73)
ECOG performance status	
0	12 (29%)
1	30 (71%)
Tumour location	
Head	21 (50%)
Body–tail	21 (50%)
CEA (ng ml^{-1})	
Median (range)	11 (1.0–62.7)
CA19-9 (U ml^{-1})	
Median (range)	2775 (1–15 620)

ECOG = Eastern Cooperative Oncology Group; CEA = carcinoembryonic antigen; CA19-9 = carbohydrate antigen 19-9.

A total of 35 patients documented disease progression at the time of analysis. The initial sites of disease progression are listed in Table 2. The pattern of failure was distant metastases in 33 patients (94%), local-regional recurrence in one patient (3%) and both in one patient (3%). The median progression-free interval and the median survival time were 4.4 and 9.5 months, respectively. The overall 1- and 2-year survival rates were 28 and 23%, respectively (Figure 1).

Toxicity

The acute toxicity is summarised in Table 3. The haematological toxicity was relatively brief and reversible in most patients. Grade 3–4 leucopenia and neutropenia occurred in 22 (52%) and 14 (33%) of the patients, respectively. Grade 3 thrombocytopenia occurred in one patient (2%) on the day after the chemoradiotherapy completion. The patient, who showed grade 4 anaemia, suffered catastrophic duodenal bleeding requiring embolisation under angiography. She exhibited cholangitis and sepsis subsequently and died on day 63.

The most common nonhaematological toxicity was anorexia, which was observed in 38 patients (90%). In total, 14 patients (33%) required intravenous hyperalimentation. In all, 33 patients (79%) complained of fatigue and one of them refused continuation of the chemoradiotherapy. Nine patients (21%) experienced grade 3 nausea. Liver function abnormality was another major adverse effect. Four patients (10%) showed grade 3 elevation of serum transaminase levels. Two of them discontinued the treatments after 19.8 and 21.6 Gy, respectively, due to serum ALT elevation of 10 times UNL according to the protocol criteria (maximum level: 452 and 435 $IU\,l^{-1}$), although the serum ALT levels of both recovered to the grade 1 levels 4 days after discontinuation of the treatment. We suspected that the ALT elevation in these two patients was gemcitabine-related toxicity because it was never reproduced after their treatment was switched over to chemoradiotherapy using 5-FU. One patient suffered unexpected acute abdominal pain requiring morphine 2 months after the completion of the chemoradiotherapy and was diagnosed with perforation of pancreatic pseudocyst into the duodenum. This pain disappeared completely by only medical management within 1 week. No patients experienced any symptoms considered to be late toxicity as of the time of analysis.

Table 2 *Patterns of initial disease progression*

Local	No. (%)
Distant metastasis	33 (94)
Peritoneum	17 (49)
Liver	15 (43)
Lymph node	1 (3)
Ovary	1 (3)
Bone	1 (3)
Local and distant metastasis	1 (3)

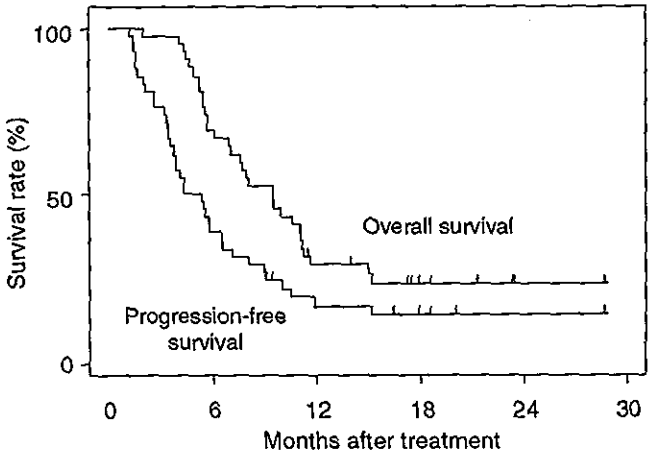

Figure 1 *Progression-free survival and overall survival curves of patients with locally advanced pancreatic cancer receiving radiotherapy with gemcitabine.*

Table 3 *Acute toxicity*

Grade	1 (%)	2 (%)	3 (%)	4 (%)
Haematological toxicity				
Leucocytopenia	3 (7)	17 (40)	21 (50)	1 (2)
Neutropenia	9 (21)	15 (36)	11 (26)	3 (7)
Thrombcoytopenia	22 (52)	2 (5)	1 (2)	0 (0)
Anaemia	21 (50)	17 (40)	0 (0)	1[a] (2)
Nonhaematological toxicity				
Total bilirubin	10 (24)	5 (12)	1 (2)	0 (0)
AST	14 (33)	5 (12)	1 (2)	0 (0)
ALT	15 (36)	11 (26)	4 (10)	0 (0)
ALP	15 (36)	5 (12)	0 (0)	0 (0)
Creatinine	0 (0)	0 (0)	0 (0)	0 (0)
Anorexia	9 (21)	5 (12)	10 (24)	14 (33)
Nausea	11 (26)	11 (26)	9 (21)	0 (0)
Vomiting	10 (24)	7 (17)	0 (0)	0 (0)
Diarrhoea	1 (2)	1 (2)	0 (0)	0 (0)
Mucositis	0 (0)	0 (0)	0 (0)	0 (0)
Duodenal ulcer	0 (0)	0 (0)	0 (0)	1[a] (2)
Fatigue	17 (40)	14 (33)	2 (5)	0 (0)
Skin rash	0 (0)	1 (2)	0 (0)	0 (0)
Infection	0 (0)	0 (0)	0 (0)	1[a] (2)

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase. [a]One patient died of duodenal bleeding and sepsis.

DISCUSSION

Based on previous randomised trials (Moertel *et al*, 1969; Gastrointestinal Tumor Study Group, 1981; Gastrointestinal Tumor Study Group, 1988), concurrent external-beam radiotherapy and 5-FU have been generally accepted as the standard treatment for locally advanced carcinomas. To intensify the treatment efficacy, various anticancer agents and radiation schedules are being investigated in clinical trials of chemoradiotherapy (Roldan *et al*, 1988; Seydel *et al*, 1990; Wagener *et al*, 1996; Thomas *et al*, 1997; Prott *et al*, 1997; Okusaka *et al*, 2001). However, marked improvement in their survival has not been observed. In an attempt to optimise radiosensitisation, radiotherapy with protracted 5-FU infusion has been examined recently, but the median survival times were similar to those observed in previous studies (Ishii *et al*, 1997).

Gemcitabine has been expected to be an agent that improves the outcome of chemoradiotherapy for locally advanced pancreatic cancer because it is a chemotherapeutic drug having meaningful palliative and prognostic impact against advanced pancreatic cancer, and it is also a potent radiosensitiser. Several experimental studies have shown that more than one mechanism leads to the potentiation of radiation-induced cell killing by gemcitabine (Lawrence *et al*, 1996; Shewach and Lawrence, 1996; van Putten *et al*, 2001). In clinics, various phase I studies for radiotherapy with gemcitabine have been conducted (McGinn *et al*, 2001; Pipas *et al*, 2001; Wolff *et al*, 2001; Ikeda *et al*, 2002; Poggi *et al*, 2002),

although the efficacy and safety of this combination have not been fully elucidated in phase II trials. A phase I trial that was conducted in our hospital determined the recommended dose of weekly gemcitabine in the phase II chemoradiotherapy trial to be 250 mg m^{-2}, because three of the six patients give a dose of 350 mg m^{-2} of gemcitabine demonstrated dose-limiting toxicities involving neutropenia/leucopenia and elevated transaminase (Ikeda *et al*, 2002).

The toxicity associated with radiotherapy with gemcitabine was relatively severe in this phase II study. Grade 3–4 leucopenia and neutropenia were observed in 52 and 33% of the patients, respectively, although none of the patients showed neutropenic fever. Nausea and anorexia were the most serious non-haematological toxicities in this treatment; 73% of the patients experienced various degrees of nausea and 33% required intravenous hyperalimentation. In all, 78% of the patients complained of general fatigue and one patient (2%) refused continuation of the treatment because of this adverse effect. These troublesome toxicities observed in this study seem to be more frequent and more severe compared with those in 5-FU-based chemoradiotherapy (Ishii *et al*, 1997). There was one death attributed to duodenal bleeding, which was arrested by transcatheter arterial embolisation, but deterioration of the general condition and lethal sepsis were induced subsequently.

The present study, in which 42 patients with locally advanced pancreatic cancer were treated with radiotherapy and weekly gemcitabine, documented a marginal impact on patient survival; the median survival time of 9.5 months is comparable to that in patients receiving conventional chemotherapy using 5-FU. However, the incidence rate of distant metastasis at the time of disease progression was remarkably higher with this treatment (97%) as compared to that with 5-FU-based chemoradiotherapy, which was reported to be 50% in our previous study (Ishii *et al*, 1997). This suggests that gemcitabine at a dose of 250 mg m^{-2} is a potent radiosensitiser for controlling local disease, but its ability as a chemotherapeutic agent is insufficient to counteract systemic tumour spread. To improve prognosis for these patients, future investigations for treatment with more systemic effects are warranted.

In an effort to increase capacity for systemic therapy, reduction of the radiation field has been attempted. Investigators at the University of Michigan elected to radiate the primary tumour alone, without the inclusion of regional lymph nodes, and administer full-dose gemcitabine concurrently, because the use of full-dose gemcitabine requires reduction of the radiation dose, based on their prior clinical experience (McGinn *et al*, 2001; Muler *et al*, 2004). Reduction of the radiation field may be one of the strategies not only for intense systemic therapy but also for decreasing the troublesome gastrointestinal toxicity often observed in our study; our recent retrospective study showed that a larger planning target volume for irradiation was only a significant predictor of severe acute intestinal toxicity in patients treated with chemoradiotherapy using gemcitabine (Ito *et al*, 2003).

Crane *et al* (2002) retrospectively compared the toxicity and efficacy of concurrent gemcitabine-based chemoradiation with those of concurrent 5-FU-based chemoradiation in patients with unresectable pancreatic cancer treated in the University of Texas MD Anderson Cancer Center. In the study, there was a significantly higher severe toxicity rate in patients treated with gemcitabine than in those with 5-FU, although the median survival times were similar between the two arms (gemcitabine *vs* 5-FU: 11 *vs* 9 months). They concluded that concurrent gemcitabine and radiotherapy could be an extremely difficult combination to administer safely, with a very narrow therapeutic index. Recently, investigators in Taiwan reported favourable results for radiotherapy with concurrent gemcitabine administration (600 mg m^2 week^{-1} for 6 weeks) in a small randomised study (Li *et al*, 2003). The gemcitabine-based chemoradiotherapy showed a significantly better median survival time (14.5 months) and a comparable toxicity profile in comparison with the 5-FU-based chemoradiotherapy (7.1 months). However, the number of enrolled patients in this study was only 16–18 in each arm. The results need further confirmation by larger multi-institutional clinical trials.

In summary, the chemoradiotherapy used in this study has a moderate activity against locally advanced pancreatic cancer and an acceptable toxicity profile, but appears to have more frequent acute toxicities compared with conventional chemoradiotherapy using 5-FU. Most patients who underwent this therapy demonstrated rapid appearance of distant metastasis. To explore innovative approaches for locally advanced pancreatic cancer, future investigations for treatment with more systemic effects and less toxicity are needed.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan. We thank Ms K Kondo for her help with the manuscript preparation.

REFERENCES

Burris III HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 15: 2403–2413

Chakravarthy A, Abrams RA (1997) Radiation therapy and 5-fluorouracil in pancreatic cancer. *Semin Radiat Oncol* 7: 291–299

Crane CH, Abbruzzese JL, Evans DB, Wolff RA, Ballo MT, Delclos M, Milas L, Mason K, Charnsangavej C, Pisters PW, Lee JE, Lenzi R, Vauthey JN, Wong AB, Phan T, Nguyen Q, Janjan NA (2002) Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? *Int J Radiat Oncol Biol Phys* 52: 1293–1302

Gastrointestinal Tumor Study Group (1981) Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads+5-fluorouracil), and high dose radiation+5-fluorouracil. *Cancer* 48: 1705–1710

Gastrointestinal Tumor Study Group (1988) Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 80: 751–755

Ikeda M, Okada S, Tokuuye K, Ueno H, Okusaka T (2002) A phase I trial of weekly gemcitabine and concurrent radiotherapy in patients with locally advanced pancreatic cancer. *Br J Cancer* 20(86): 1551–1554

Ishii H, Okada S, Tokuuye K, Nose H, Okusaka T, Yoshimori M, Nagahama H, Sumi M, Kagami Y, Ikeda H (1997) Protracted 5-fluorouracil infusion with concurrent radiotherapy as a treatment for locally advanced pancreatic carcinoma. *Cancer* 79: 1516–1520

Ito Y, Okusaka T, Kagami Y, Ueno H, Ikeda M, Sumi M, Imai A, Ikeda H (2003) Evaluation of acute intestinal toxicity in relation to the volume of irradiated small bowel in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 57: S383–4

Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 63: 457–481

Lawrence TS, Chang EY, Hahn TM, Hertel LW, Shewach DS (1996) Radiosensitization of pancreatic cancer cells by 2′,2′-difluoro-2′-deoxycytidine. *Int J Radiat Oncol Bio Phys* 34: 867–872

Lawrence TS, Chang EY, Hahn TM, Shewach DS (1997) Delayed radiosensitization of human colon carcinoma cells after a brief exposure to 2′,2′-difluoro-2′-deoxycytidine (Gemcitabine). *Clin Cancer Res* 3: 777–782

Li CP, Chao Y, Chi KH, Chan WK, Teng HC, Lee RC, Chang FY, Lee SD, Yen SH (2003) Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. *Int J Radiat Oncol Biol Phys* 57: 98–104

McGinn CJ, Zalupski MM, Shureiqi I, Robertson JM, Eckhauser FE, Smith DC, Brown D, Hejna G, Strawderman M, Normolle D, Lawrence TS (2001) Phase I trial of radiation dose escalation with concurrent weekly full-dose gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 19: 4202–4208

Moertel CG, Childs Jr DS, Reitemeier RJ, Colby Jr MY, Holbrook MA (1969) Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* 2: 865–867

Muler JH, McGinn CJ, Normolle D, Lawrence T, Brown D, Hejna G, Zalupski MM (2004) Phase I trial using a time-to-event continual reassessment strategy for dose escalation of cisplatin combined with gemcitabine and radiation therapy in pancreatic cancer. *J Clin Oncol* 22: 238–243

Okada S (1999) Non-surgical treatments of pancreatic cancer. *Int J Clin Oncol* 4: 257–266

Okusaka T, Okada S, Tokuuye K, Wakasugi H, Saisho H, Ishikawa O, Matsuno S, Sato T, Sato K (2001) Lack of effectiveness of radiotherapy combined with cisplatin in patients with locally advanced pancreatic carcinoma. *Cancer* 91: 1384–1389

Pipas JM, Mitchell SE, Barth Jr RJ, Vera-Gimon R, Rathmann J, Meyer LP, Wagman RS, Lewis LD, McDonnell C, Colacchio TA, Perez RP (2001) Phase I study of twice-weekly gemcitabine and concomitant external-beam radiotherapy in patients with adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys* 50: 1317–1322

Poggi MM, Kroog GS, Russo A, Muir C, Cook J, Smith J, Mitchell JB, Herscher LL (2002) Phase I study of weekly gemcitabine as a radiation sensitizer for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 54: 670–676

Prott FJ, Schonekaes K, Preusser P, Ostkamp K, Wagner W, Micke O, Potter R, Sulkowski U, Rube C, Berns T, Willich N (1997) Combined modality treatment with accelerated radiotherapy and chemotherapy in patients with locally advanced inoperable carcinoma of the pancreas: results of a feasibility study. *Br J Cancer* 75: 597–601

Roldan GE, Gunderson LL, Nagorney DM, Martin JK, Ilstrup DM, Holbrook MA, Kvols LK, McIlrath DC (1988) External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. *Cancer* 61: 1110–1116

Seydel HG, Stablein DM, Leichman LP, Kinzie JJ, Thomas PR (1990) Hyperfractionated radiation and chemotherapy for unresectable localized adenocarcinoma of the pancreas. The Gastrointestinal Tumor Study Group experience. *Cancer* 65: 1478–1482

Shewach DS, Lawrence TS (1996) Gemcitabine and radiosensitization in human tumor cells. *Invest New Drugs* 14: 257–263

Thomas Jr CR, Weiden PL, Traverso LW, Thompson T (1997) Concomitant intraarterial cisplatin, intravenous 5-flourouracil, and split-course radiation therapy for locally advanced unresectable pancreatic adenocarcinoma: a phase II Study of 16th Puget Sound Oncology Consortium (PSOC-703). *Am J Clin Oncol* 20: 161–165

van Putten JWG, Groen HJM, Smid K, Peters GJ, Kampinga HH (2001) End-joining deficiency and radiosensitization induced by gemcitabine. *Cancer Res* 61: 1585–1591

Wagener DJ, Hoogenraad WJ, Rougier P, Lusinchi A, Taal BG, Veenhof CH, de Graeff A, Conroy T, Curran D, Sahmoud T, Wils J (1996) Results of a phase II trial of epirubicin and cisplatin (EP) before and after irradiation and 5-fluorouracil in locally advanced pancreatic cancer: an EORTC GITCCG study. *Eur J Cancer* 32A: 1310–1313

Wolff RA, Evans DB, Gravel DM, Lenzi R, Pisters PW, Lee JE, Janjan NA, Charnsangavej C, Abbruzzese JL (2001) Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. *Clin Cancer Res* 7: 2246–2253

World Health Organization (1979) *WHO Handbook for Reporting Results of Cancer Treatment*, Offset Publication 48 Geneva: World Health Organization

Clinical Study

Oncology

Oncology 2004;67:215–221
DOI: 10.1159/000081320

Received: December 12, 2003
Accepted after revision: March 11, 2004

Phase I Study of Hyperfractionated Radiation Therapy with Protracted 5-Fluorouracil Infusion in Patients with Locally Advanced Pancreatic Cancer

Hideki Ueno[a] Takuji Okusaka[a] Masafumi Ikeda[a] Koich Tokuuye[b]

Divisions of [a]Hepatobiliary and Pancreatic Oncology, and [b]Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Key Words
Chemoradiotherapy · 5-Fluorouracil · Hyperfractionation · Pancreatic cancer · Phase I study · Radiation therapy

Abstract
Objective: This study investigated the maximum-tolerated dose of hyperfractionated radiation therapy with protracted 5-fluorouracil (5-FU) infusion in patients with locally advanced, unresectable pancreatic cancer. ***Methods:*** Five cohorts of patients were scheduled to receive escalating doses of hyperfractionated radiation therapy (range, 45.6–64.8 Gy). All patients received two fractions of 1.2 Gy each (separated by 6 h) per day for 5 days a week, and received protracted 5-FU infusion (200 mg/m^2/day) during the radiation course. The maximum-tolerated dose was defined as one dose level below the dose at which more than one third of 3–6 patients experienced dose-limiting toxicity. ***Results:*** Twenty-nine patients were enrolled in this study. The most common toxicities were nausea/vomiting and anorexia. Although 1 patient developed bleeding from a gastric ulcer 3 months after the completion of chemoradiotherapy, the maximum-tolerated dose was not reached even at the highest dose level (level 5, 64.8 Gy). The median survival time was 12.2 months and the 1-year survival rate was 55.0%. ***Conclusion:*** The toxicity associated with our regimen was tolerable up to dose level 5 (64.8 Gy). We are currently conducting a phase II study of this hyperfractionated radiation therapy with protracted 5-FU infusion at a dose of 64.8 Gy.

Introduction

Because of the difficulty in diagnosing pancreatic cancer early, the vast majority of patients have unresectable disease at the time of diagnosis. About 30–50% of the unresectable cases have localized disease without distant metastases. In the treatment of locally advanced, unresectable pancreatic cancer, radiotherapy with concomitant chemotherapy has been the treatment of choice since it offers better survival rates when compared to treatment by radiotherapy or chemotherapy alone [1, 2]. However, improvement in chemoradiotherapy for pancreatic cancer is necessary because chemoradiotherapy has achieved only modest improvements in median survival and minimal increases in long-term survival [3].

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–2414/04/0674–0215$21.00/0

Accessible online at:
www.karger.com/oci

Hideki Ueno, MD
Hepatobiliary and Pancreatic Oncology Division
National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku
Tokyo 104-0045 (Japan)
Tel. +81 3 3542 2511, Fax +81 3 3542 3815, E-Mail hueno@ncc.go.jp

Hyperfractionation, the administration of a larger number of smaller doses per fraction, is one of the promising and tempting alternatives to conventional radiation therapy. One possible advantage of hyperfractionation is that this approach may permit an improvement in tumor control by increasing the total tumor dose without increasing the risk of late complications [4]. Several encouraging results of this therapeutic modality have been reported in patients with head and neck cancer or lung cancer [5, 6]. However, only limited information about hyperfractionated radiation therapy is available for pancreatic cancer. Therefore, we conducted a phase I study of hyperfractionated radiation therapy with 5-fluorouracil (5-FU) in patients with locally advanced pancreatic cancer. In the present study, 5-FU was administered by protracted infusion during the radiation course to intensify the anti-tumor effect of chemotherapy. The primary objective of this study was to assess the toxicity of hyperfractionated radiation therapy with protracted 5-FU infusion and to determine the maximum-tolerated dose of radiation in this combined treatment.

Patients and Methods

Patients

Eligibility criteria included (1) locally advanced unresectable pancreatic cancer; (2) histologically or cytologically confirmed adenocarcinoma of the pancreas; (3) 20–74 years of age; (4) an Eastern Cooperative Oncology Group performance status of 0–2, and (5) no prior anti-cancer treatment. Required pretreatment laboratory data included white blood cell count ≥4,000/μl, hemoglobin level ≥10 g/dl, platelet count ≥100,000/μl, normal serum creatinine level, serum total bilirubin level ≤2.0 mg/dl, serum albumin level ≥3.0 g/dl and serum transaminase level ≤2.5 × upper normal limit. Exclusion criteria were: concomitant malignancy; pleural and/or peritoneal effusion; active ulcer of the gastrointestinal tract; active infection; severe heart disease; pregnant or lactating females, or other serious medical conditions. A chest X-ray and abdominal computed tomography (CT) were performed on all patients before treatment. The disease was considered locally advanced if abdominal CT revealed celiac trunk and/or superior mesenteric artery encasements with no evidence of systemic metastasis. Diagnostic laparoscopy was not performed. Histological and/or cytological confirmation was obtained by needle biopsy. Endoscopic or percutaneous biliary drainage was performed before treatment in patients with obstructive jaundice. This protocol was approved by the Institutional Review Board of the National Cancer Center. All patients received a full explanation of this study and gave written informed consent before entry into the study.

Treatment

The study design consisted of a sequential dose escalation of radiation therapy. The radiation dose level was planned in five cohorts as shown in table 1. The starting dose of radiation was 45.6 Gy, deemed safe based on the results of previous studies of hyperfractionation for pancreatic cancer [7–9]. Dose escalations at 4.8-Gy increments were planned if the previous dose had been tolerated. All patients received two fractions of 1.2 Gy each (separated by 6 h) per day for 5 days a week using 10–14 MV X-rays from a microtron (MM22, Scanditronix, Uppsala, Sweden). Treatment planning was determined by a three-dimensional treatment planner (FOCUS, Computerized Medical Systems, St. Louis, Mo., USA). Contours of the clinical target volume, which included the primary tumor, regional lymph nodes detected by CT, and paraaortic regions at celiac and supramesenteric axes were manually outlined on serial CT images displayed on a monitor. The definition of the regional lymph nodes followed the 6th edition of the UICC TNM Classification. Paraaortic lymph node metastasis was considered distant metastasis. A planning target volume which included a 10-mm margin of normal tissue surrounding the clinical target volume was defined on each CT image and on the craniocaudal dimension. Four field techniques (anterior, posterior and opposed lateral fields) were used. Spinal cord dose was maintained below 45 Gy, ≥50% of liver was limited to ≤30 Gy, and ≥50% of both kidneys were limited to ≤20 Gy. Chemotherapy consisted of protracted infusion of 5-FU at a dose of 200 mg/m^2/day, which began on the first day of radiation and continued through the entire radiation course. One week after the completion of chemoradiotherapy, maintenance chemotherapy of 5-FU (500 mg/m^2, drip infusion) was given weekly until disease progression or unacceptable toxicity.

The toxicity of the treatment was scored according to the criteria of the Japan Society for Cancer Therapy [10], which are fundamentally similar to the National Cancer Institute common toxicity criteria. Both radiation therapy and chemotherapy were suspended for grade 3 hematological toxicity or grade 2 non-hematological toxicity excluding nausea/vomiting and anorexia during the treatment course, and treatment was restarted when toxicity was resolved. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 non-hematological toxicities (excluding nausea/vomiting and anorexia) or grade 4 hematological toxicity occurring during chemoradiotherapy or within 4 weeks after completing treatment. If both radiation therapy and chemotherapy were suspended for more than 10 days due to adverse effects, the adverse effects were considered DLT.

Table 1. Dose-escalation scheme for maximum-tolerated doses in hyperfractionated radiation therapy

Study cohort	Dose/fraction Gy	Total fractions	Total dose, Gy	Treatment duration, days
1	1.2	38	45.6	25
2	1.2	42	50.4	29
3	1.2	46	55.2	31
4	1.2	50	60.0	33
5	1.2	54	64.8	37

Treatment duration is given from the first day to the last day of radiation.

Radiation dose escalation was scheduled to proceed as follows. Initially, 3 patients were to be studied in cohort 1. If none of the initial 3 patients in a cohort experienced DLT, the radiation dose was to be increased in the next 3 patients according to the schedules listed in table 1. If 1 or 2 of the initial 3 patients in a cohort experienced DLT, a maximum of 3 additional patients were entered into the cohort. If only 1 or 2 of 6 patients experienced DLT, dose escalation would continue. If 3 or more patients experienced DLT at a given dose level, then the previous dose level would be considered maximum-tolerated dose. Dose escalation to the next cohort was allowed after observing a previous cohort for a minimum of 4 weeks after the completion of chemoradiotherapy.

Follow-up CT was performed every 2 months to assess objective tumor response according to World Health Organization criteria [11]. Progression-free and overall survival were measured from the 1st day of study entry, and the survival rate was calculated by the Kaplan-Meier method. Serum CA 19-9 levels were measured monthly by radioimmunometric assay using the Centocor radioimmunoassay kit (Centocor, Malvern, Pa., USA).

Table 2. Patient characteristics (n = 29)

Characteristics	Patients	
	n	%
Gender		
Men	17	59
Women	12	41
Performance status		
0	5	17
1	24	83
Biliary drainage	7	24
Tumor location		
Head	9	31
Body-tail	20	69

Median carcinoembryonic antigen was 2.9 ng/ml (range: 0.9–42.1) and median CA 19-9 429 U/ml (range: 1–16,680). Median age of the patients was 59 years (range 32–74).

Results

Patient Characteristics

Between April 1999 and May 2001, 29 patients with locally advanced, unresectable pancreatic cancer were enrolled in the study at the National Cancer Center Hospital, Tokyo, Japan. The demographic characteristics of the 29 patients are listed in table 2. Relatively many patients with pancreatic body-tail cancer were enrolled in the study. All patients were in stage III according to the UICC TNM Classification (ed 6).

Toxicities

All 29 patients were assessable for toxicity. Two of the 29 patients failed to complete chemoradiotherapy for reasons other than toxicity: 1 patient at dose level 1 abandoned treatment after 25.2 Gy because of disease progression, and another patient at dose level 3 refused to continue treatment after 50.4 Gy, although there were no clinically significant adverse effects. Of the 27 patients evaluable for DLT, 22 (81%) completed the scheduled course of chemoradiotherapy. However, the remaining 5 had to abandon treatment because of adverse effects: nausea/vomiting and anorexia (3 patients), alanine aminotransferase elevation (1 patient) and thrombocytopenia (1 patient). Table 3 shows the toxicities that occurred during chemoradiotherapy or within 4 weeks after completing treatment. Hematological toxicity was relatively mild and reversible. Two patients exhibited grade 3 neutropenia, but these toxicities recovered immediately after interruption of chemoradiotherapy. Although thrombocytopenia was a rare toxicity, 1 patient at level 5 showed grade 4 thrombocytopenia after 52.8 Gy. Since this thrombocytopenia persisted after discontinuation of chemoradiotherapy, bone marrow aspiration was performed, and the patient was diagnosed with myelodysplastic syndrome. The most common non-hematological toxicities were nausea/vomiting and anorexia, which were observed in 27 (93%) and 24 patients (83%), respectively. These adverse effects were generally mild to moderate, but 5 patients required temporary treatment interruption (median, 2 days; range, 2–5 days) and 3 patients abandoned chemoradiotherapy because of prolonged toxicities. Other non-hematological toxicities included diarrhea and liver dysfunction, but these were also generally mild and transient. During the median follow-up period of 8.2 months (range, 1.7–26 months), late radiation-related toxicity was observed in only 1 patient, who developed bleeding from a gastric ulcer 3 months after the completion of chemoradiotherapy (level 1, 45.6 Gy) and then recovered from the ulcer by conservative treatment. There were no life-threatening toxicities, and no treatment-related deaths occurred. Table 4 summarizes the DLT observed in the current study. The maximum-tolerated dose of this phase I study was not reached even at the highest dose level (level 5, 64.8 Gy).

Therapeutic Results and Patient Outcome

Six patients (21%) achieved a partial response, 19 (66%) remained stable and 4 (14%) showed progressive disease demonstrated by the development of distant metastases. The serum CA 19-9 level was reduced more than

Table 3. Treatment-related toxicity (n = 29)

Toxicities	Study cohort														
	1 45.6 Gy (n = 6)			2 50.4 Gy (n = 3)			3 55.2 Gy (n = 7)			4 60.0 Gy (n = 6)			5 64.8 Gy (n = 7)		
	1, 2	3	4	1, 2	3	4	1, 2	3	4	1, 2	3	4	1, 2	3	4
Hematological															
Anemia	1	0	0	0	0	0	4	0	0	0	0	0	0	0	0
Leukocytopenia	3	0	0	3	0	0	6	1	0	3	0	0	4	0	0
Neutropenia	3	0	0	2	0	0	2	2	0	2	0	0	1	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	2	0	0	0	0	1
Non-hematological															
Anorexia	2	3	0	2	0	0	4	3	0	1	3	0	3	3	0
Nausea/vomiting	5	0	0	3	0	0	7	0	0	3	2	0	7	0	0
Diarrhea	1	0	0	1	0	0	1	1	0	1	0	0	3	0	0
Stomatitis	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
AST/ALT	3	0	0	1	0	0	3	0	0	1	1	0	2	0	0
Alkaline phosphatase	1	0	0	0	0	0	1	0	0	2	0	0	0	0	0
Skin rash	1	0	0	0	0	0	2	0	0	1	0	0	0	0	0
Abdominal pain	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Fatigue	3	1	0	2	0	0	5	0	0	4	0	0	5	0	0
Weight loss	0	0	0	1	0	0	2	0	0	2	0	0	1	0	0

AST = Aspartate aminotransferase; ALT = alanine aminotransferase.

Table 4. Dose-limiting toxicity (n = 27)

Study cohort	Patients	Patients with DLT	DLT	Total dose at DLT, Gy
1 (45.6 Gy)	6[a]	1	suspension of treatment for >10 days[b]	31.2
2 (50.4 Gy)	3	0		
3 (55.2 Gy)	6	2	suspension of treatment for >10 days[b]	36.0
			grade 3 diarrhea	55.2
4 (60.0 Gy)	6	2	suspension of treatment for >10 days[b]	31.2
			grade 3 ALT elevation	46.8
5 (64.8 Gy)	6	1	grade 4 thrombocytopenia	52.8

ALT = Alanine aminotransferase.
[a] One patient developed gastric ulcer 3 months after the completion of chemoradiotherapy.
[b] Due to nausea/vomiting and anorexia.

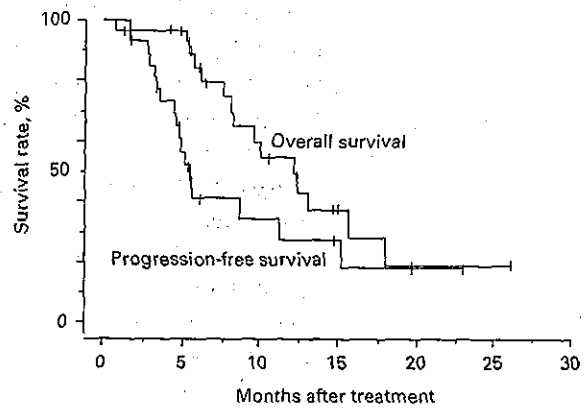

Fig. 1. Overall survival curve and progression-free curve of 29 patients who received hyperfractionated radiotherapy with protracted 5-FU infusion for locally advanced pancreatic cancer. Vertical lines indicate censored cases.

Table 5. Patterns of initial disease progression

Progression	Patients	
	n	%
None	10	34
Local	2	7
Distant	15	52
Liver	8	
Lymph nodes	3	
Peritoneum	1	
Liver and peritoneum	2	
Lung and peritoneum	1	
Local and distant[a]	2	7

[a] Peritoneum.

50% in 12 (55%) of 22 patients who had a pretreatment level of 100 U/ml or greater. Disease progression and death from cancer were documented in 19 and 13 patients, respectively, at the time of analysis. The initial sites of disease progression are listed in table 5. Distant metastases predominated over local progression. The median progression-free time and 1-year progression-free rate were 5.4 months and 20.2%, respectively. The median survival time (MST) and 1-year survival rate were 12.2 months and 55.0%, respectively (fig. 1).

Discussion

Based on previous randomized trials, concurrent external-beam radiotherapy and chemotherapy have been the treatment of choice for locally advanced, unresectable pancreatic cancer [1, 2]. Nevertheless, there is substantial room for improvement in chemoradiotherapy for pancreatic cancer because chemoradiotherapy has achieved only modest improvements in median survival and minimal increase in long-term survival to date [3]. Therefore, there is a clear need to establish more effective chemoradiotherapy for locally advanced pancreatic cancer.

Since local relapse of disease after chemoradiotherapy remains high, local tumor control and systemic chemotherapy are necessary for locally advanced pancreatic cancer. To intensify local tumor control, numerous clinical trials have been performed with specialized radiotherapy techniques, including intraoperative radiotherapy, brachytherapy, high-dose conformal radiotherapy and hyperfractionated radiation therapy [7–9, 12–15]. It is noteworthy that relatively good local tumor control and survival were achieved in these trials in which a higher dose was given using external-beam radiotherapy combined with either intraoperative radiotherapy or brachytherapy. These findings suggest the efficacy of dose-intensive radiotherapy for locally advanced pancreatic cancer.

Hyperfractionation is expected to produce a differential effect between the response in tumor and normal tissues. The basic rationale of hyperfractionation is that the use of small dose fractions allows higher total doses to be administered within the tolerance of late-responding normal tissues and that this translates to a higher biologically effective dose to the tumor [4]. Other rationales for hyperfractionation are radiosensitization through redistribution and reduced dependence on oxygen effect [4, 16, 17]. Clinical trials have demonstrated that hyperfractionated radiotherapy has a favorable treatment efficacy in some types of tumors, including head and neck cancer and lung cancer [5, 6].

With regard to pancreatic cancer, however, only limited information about hyperfractionated radiation is available. In 1990, the Gastrointestinal Tumor Study Group reported on hyperfractionated radiation therapy in patients with locally advanced pancreatic cancer [7]. In this study, 18 patients received two fractions of 1.2 Gy each per day (total 50.4 Gy) and bolus 5-FU infusion (350 mg/m^2) on the first 3 and last 3 days of radiation therapy. However, the study results were not encouraging: the MST and 1-year survival rate were 35 weeks and

Table 6. Comparison of toxicity, response rate and MST

Toxicity and response	Patients, n (%)	
	current study (n = 29)	conventional regimen (n = 20)
≥ Grade 2 toxicity		
Leukocytopenia	8 (28)	4 (20)
Thrombocytopenia	1 (3)	0 (0)
Nausea/vomiting	21 (72)	3 (15)
Diarrhea	2 (7)	0 (0)
Stomatitis	0 (0)	3 (15)
ALT elevation	5 (17)	2 (10)
Response rate	6 (21)	2 (10)

MST was *12.2* months in the current study and *10.4* months in patients treated with the conventional regimen. ALT = Alanine aminotransferase.

39%, respectively. Prott et al. [8] treated 32 patients with locally advanced pancreatic cancer by hyperfractionated radiation therapy (total 44.8 Gy) along with 5-FU and leucovorin (MST, 12.7 months), and Luderhoff et al. [9] conducted a pilot study using a combination of hyperfractionated radiation (total 45–50 Gy) and continuous infusion of 5-FU in 13 patients (MST, 36 weeks). Summarizing these three trials, although toxicities seemed to be acceptable, improved survival was unfortunately not achieved. However, the total dose of radiation used in these trials might have been insufficient to obtain adequate local tumor control. Therefore, in the current study, we conducted a phase I study, and concluded that the toxicity associated with our regimen was tolerable up to a total dose of 64.8 Gy. Our conclusions were consistent with the results of the recent phase I–II study for locally advanced pancreatic cancer, in which Ashamalla et al. [18] reported that the use of hyperfractionated radiotherapy (2 fractions of 1.1 Gy each per day) to a dose of 63.8 Gy combined with weekly paclitaxel was tolerated. They also reported that good local control was observed following their regimen; complete relief of pain was achieved in 10 of 14 patients, and objective response was achieved in 5 of 17 evaluable patients.

The adverse effects associated with our regimen seemed to be tolerable. There were no life-threatening toxicities, and no treatment-related deaths occurred. However, acute reactions such as gastrointestinal toxicity were more severe compared with conventional regimens of chemoradiotherapy. Table 6 shows a comparison of adverse effects between our hyperfractionated chemoradiotherapy and the conventional chemoradiotherapy previously performed in our hospital, which consisted of protracted 5-FU infusion (200 mg/m^2/day) with current radiation therapy (50.4 Gy in 28 fractions over 5.5 weeks) [19]. Although hematological toxicity did not significantly differ between these two regimens, nausea/vomiting were more frequently observed in the hyperfractionated chemoradiotherapy. As a result, 8 of 29 (28%) patients treated by hyperfractionated chemoradiotherapy required treatment interruption due to gastrointestinal toxicities, and 3 of the 8 patients abandoned chemoradiotherapy. It is interesting that these 3 patients developed such gastrointestinal toxicities before reaching a total radiation dose of 40 Gy (31.2, 36.0, and 31.2 Gy, respectively). Therefore, although this schedule of hyperfractionated radiation therapy was acceptable for most patients with pancreatic cancer, some patients developed severe and/or prolonged acute toxicities at a relatively low total radiation dose. There was no significant association between the gastrointestinal toxicities and pretreatment factors including gender, age, performance status, and tumor location (data not shown).

In the current study, relatively good local tumor control was obtained: 6 patients (21%) achieved a partial response and 19 (66%) remained stable. At the time of analysis, local disease progression had occurred in only 4 (14%) patients. In addition, the MST of 12.2 months was equal or superior to that of previous studies using conventional fractionation [1, 2, 19]. These findings have encouraged us to conduct further trials of hyperfractionated chemoradiotherapy. However, the incidence of distant metastasis did not decrease after treatment in the present study. Therefore, more effective systemic therapy will be necessary to reduce distant metastases and subsequently improve long-term survival.

In conclusion, the toxicity associated with our regimen was tolerable up to dose level 5 (64.8 Gy). Hoping to demonstrate a superior survival benefit for patients with locally advanced pancreatic cancer, we are currently conducting a phase II trial of this hyperfractionated radiation therapy with protracted 5-FU infusion at a dose of 64.8 Gy.

References

1 Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO Jr, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW: Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6,000 rads) radiation alone, moderate dose radiation (4,000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981;48:1705–1710.

2 Gastrointestinal Tumor Study Group: Treatment of locally unresectable carcinoma of the pancreas: Comparison of combined modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst 1988; 80:751–755.

3 Okada S: Non-surgical treatments of pancreatic cancer. Int J Clin Oncol 1999;4:257–266.

4 Ang KK, Thames HD, Peters LJ, Perez C: Altered fractionation schedules; in Perez CA, Brady L (eds): Principles and Practice of Radiation Oncology. Philadelphia, Lippincott-Raven, 1997, pp 119–142.

5 Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, Gardani G, Van Den Bogaert W, Danczak S, Bolla M, et al: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 1992; 25:231–241.

6 Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF: A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: Possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: Report of Radiation Therapy Oncology Group 83-11. J Clin Oncol 1990; 8:1543–1555.

7 Seydel HG, Stablein DM, Leichman LP, Kinzie JJ, Thomas PR: Hyperfractionated radiation and chemotherapy for unresectable localized adenocarcinoma of the pancreas. The Gastrointestinal Tumor Study Group experience. Cancer 1990;65:1478–1482.

8 Prott FJ, Schonekaes K, Preusser P, Ostkamp K, Wagner W, Micke O, Potter R, Sulkowski U, Rube C, Berns T, Willich N: Combined modality treatment with accelerated radiotherapy and chemotherapy in patients with locally advanced inoperable carcinoma of the pancreas: Results of a feasibility study. Br J Cancer 1997; 75:597–601.

9 Luderhoff EC, Gonzalez Gonzalez D, Bakker P: Pilot study in locally advanced unresectable pancreas carcinoma using a combination of accelerated radiotherapy and continuous infusion of 5-fluorouracil. Radiother Oncol 1996; 40:241–243.

10 Japan Society for Cancer Therapy: Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. J Jpn Soc Cancer Ther 1993;28:101–130.

11 World Health Organization: WHO handbook for Reporting Results of Cancer Treatment. Offset Publication 48. Geneva, World Health Organization, 1979.

12 Roldan GE, Gunderson LL, Nagorney DM, Martin JK, Ilstrup DM, Holbrook MA, Kvols LK, McIlrath DC: External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. Cancer 1988;61:1110–1116.

13 Nishimura Y, Hosotani R, Shibamoto Y, Kokubo M, Kanamori S, Sasai K, Hiraoka M, Ohshio G, Imamura M, Takahashi M, Abe M: External and intraoperative radiotherapy for resectable and unresectable pancreatic cancer: Analysis of survival rates and complications. Int J Radiat Oncol Biol Phys 1997;39:39–49.

14 Mohiuddin M, Rosato F, Barbot D, Schuricht A, Biermann W, Cantor R: Long-term results of combined modality treatment with ^{125}I implantation for carcinoma of the pancreas. Int J Radiat Oncol Biol Phys 1992;23:305–311.

15 Ceha HM, van Tienhoven G, Gouma DJ, Veenhof CH, Schneider CJ, Rauws EA, Phoa SS, Gonzalez Gonzalez D: Feasibility and efficacy of high dose conformal radiotherapy for patients with locally advanced pancreatic carcinoma. Cancer 2000;89:2222–2229.

16 Withers HR: Cell cycle redistribution as a factor in multifraction irradiation. Radiology 1975;114:199–202.

17 Palcic B, Skarsgard LD: Reduced oxygen enhancement ratio at low doses of ionizing radiation. Radiat Res 1984;100:328–339.

18 Ashamalla H, Zaki B, Mokhtar B, Colella F, Selim H, Krishnamurthy M, Ross P: Hyperfractionated radiotherapy and paclitaxel for locally advanced/unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2003;55: 679–687.

19 Ishii H, Okada S, Tokuuye K, Nose H, Okusaka T, Yoshimori M, Nagahama H, Sumi M, Kagami Y, Ikeda H: Protracted 5-fluorouracil infusion with concurrent radiotherapy as a treatment for locally advanced pancreatic carcinoma. Cancer 1997;79:1516–1520.

British Journal of Cancer (2004) 91, 1769–1774

www.bjcancer.com

Phase II study of S-1 in patients with advanced biliary tract cancer

H Ueno*[,1], T Okusaka[1], M Ikeda[1], Y Takezako[1] and C Morizane[1]

[1]*Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

Clinical

The aim of this study was to investigate the efficacy and safety of an oral fluoropyrimidine derivative, S-1, in patients with advanced biliary tract cancer. Patients with pathologically confirmed advanced biliary tract cancer, a measurable lesion, and no history of radiotherapy or chemotherapy were enrolled. S-1 was administered orally (40 mg m^{-2} b.i.d.) for 28 days, followed by a 14-day rest period. A pharmacokinetic study was performed on day 1 in the initial eight patients. In all, 19 consecutive eligible patients were enrolled in the study between July 2000 and January 2002. The site of the primary tumour was the gallbladder ($n=16$), the extrahepatic bile ducts ($n=2$), and the ampulla of Vater ($n=1$). A median of two courses of treatment (range, 1–12) was administered. Four patients achieved a partial response, giving an overall response rate of 21.1%. The median time-to-progression and median overall survival period were 3.7 and 8.3 months, respectively. Although grade 3 anorexia and fatigue occurred in two patients each (10.5%), no grade 4 toxicities were observed. The pharmacokinetic parameters after a single oral administration of S-1 were similar to those of patients with other cancers. S-1 exhibits definite antitumour activity and is well tolerated in patients with advanced biliary tract cancer.

British Journal of Cancer (2004) **91**, 1769–1774. doi:10.1038/sj.bjc.6602208 www.bjcancer.com
Published online 26 October 2004

Keywords: S-1; phase II study; biliary tract cancer; chemotherapy; pharmacokinetics

The incidence of biliary tract cancer has been steadily increasing in Japan over the past several decades (Okusaka, 2002). Currently, biliary tract cancer is the sixth leading cause of death from cancer in Japan, with statistics from 2002 indicating a total of about 16 000 deaths from this disease. As a result of the lack of characteristic early symptoms, biliary tract cancers are often diagnosed at an advanced stage, and the prognosis of patients with advanced biliary tract cancer is dismal. Although systemic treatment is used for advanced disease, the impact of existing chemotherapy is virtually negligible. A large number of agents, including 5-fluorouracil (5-FU), mitomycin-C, and cisplatin, have been tested as single agents or in combination therapies without appreciable efficacy (Hejna *et al*, 1998; van Riel *et al*, 1999; Yee *et al*, 2002). Although recent clinical studies have suggested the potential activity of gemcitabine for the treatment of biliary tract cancer, producing response rates of 8 to 36% (Mezger *et al*, 1998; Raderer *et al*, 1999; Gallardo *et al*, 2001; Gebbia *et al*, 2001; Kubicka *et al*, 2001; Penz *et al*, 2001; Tsavaris *et al*, 2004), studies on a larger scale are needed to confirm its efficacy. In any case, to improve the prognosis of patients with biliary tract cancer, a clear need exists for new, effective chemotherapeutic agents.

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 (Shirasaka *et al*, 1996a). 5-chloro-2,4-dihydroxypyridine 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 tumour tissues (Tatsumi *et al*, 1987). Oteracil potassium, 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 (Shirasaka *et al*, 1993). S-1 therapy in athymic nude rats was associated with the retention of a higher and more prolonged concentration of 5-FU in plasma and tumour tissues, when compared with UFT (Shirasaka *et al*, 1996b). The antitumour effect of S-1 has been already demonstrated in a variety of solid tumours: the response rates for advanced gastric cancer (Sakata *et al*, 1998; Koizumi *et al*, 2000), colorectal cancer (Ohtsu *et al*, 2000), non-small-cell lung cancer (Kawahara *et al*, 2001), and head and neck cancer (Inuyama *et al*, 2001) in the late phase II studies conducted in Japan were 44–49, 35, 22, and 29%, respectively. In addition, a recent early phase II study for advanced pancreatic cancer demonstrated a response rate of 21% in 19 patients (Okada *et al*, 2002). The efficacy of S-1 for the treatment of gastrointestinal cancer has also been reported in European patients: the response rates for advanced gastric cancer (Chollet *et al*, 2003) and colorectal cancer (Van den Brande *et al*, 2003) were 32 and 24%, respectively. However, no previous reports have described the efficacy and safety of S-1 for the treatment of biliary tract cancer. Consequently, the present early phase II study was conducted to evaluate the efficacy and safety of S-1 in patients with advanced biliary tract cancer.

PATIENTS AND METHODS

Patients

Patients were required to meet the following eligibility criteria: histologically or cytologically confirmed advanced biliary tract cancer; at least one measurable lesion; no history of prior

*Correspondence: Dr H Ueno; E-mail: hiueno@ncc.go.jp
Received 24 May 2004; revised 2 September 2004; accepted 6 September 2004; published online 26 October 2004

antitumour treatment except resection; a Karnofsky performance status (KPS) of 80–100 points; age of 20–74 years; an estimated life expectancy of at least 2 months; adequate organ function, defined as a white blood cell count of 4000–12 000 mm^{-3}, a platelet count $\geqslant 100\,000\ mm^{-3}$, a haemoglobin level $\geqslant 10.0$ g/dl, a normal serum creatinine level, a serum total bilirubin level $\leqslant 3$ times the upper limit of normal, an aspartate aminotransferase and alanine aminotransferase level $\leqslant 2.5$ times the upper limits of normal; and written informed consent. Patients who had obstructive jaundice were considered eligible if their bilirubin level could be reduced to within 3 times the upper limit of normal after biliary drainage. The exclusion criteria were as follows: a history of drug hypersensitivity; severe complications, such as infection, heart disease, and renal disease; symptomatic metastasis of the central nervous system; active concomitant malignancy; marked pleural effusion or ascites; watery diarrhoea; and pregnancy or lactation. This study was approved by the institutional review board at the National Cancer Center and conducted in accordance with the Good Clinical Practice guidelines of Japan.

Clinical

Treatments

S-1 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}; $1.25\ m^2 \leqslant$ BSA $< 1.50\ m^2$, 100 mg day^{-1}; and $1.50\ m^2 \leqslant$ BSA, 120 mg day^{-1}. 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, the temporary interruption of the S-1 administrations was allowed until the toxicity subsided to grade 1 or less. If the daily dose of S-1 was considered to be intolerable, the retreatment dose was reduced by 20 mg day^{-1} (minimum dose, 80 mg day^{-1}). If no toxicity occurred, the rest period shortened to 7 days was allowed. 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. S-1 was provided by Taiho Pharmaceutical Co. Ltd (Tokyo, Japan).

Response and toxicity evaluation

The response after each course was assessed according to the Japan Society for Cancer Therapy Criteria (Japan Society for Cancer Therapy, 1993), which is similar to the World Health Organization Criteria. Briefly, a complete response (CR) was defined as the disappearance of all clinical evidence of the tumour for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions for a minimum of 4 weeks. No change (NC) was defined as a reduction of less than 50% or a less than 25% increase in the sum of the products of two perpendicular diameters of all lesions for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase of 25% or more in the sum of the products of two perpendicular diameters of all lesions, the appearance of any new lesion, or a deterioration in the clinical status that was consistent with disease progression. Primary bile duct lesions were not considered to be measurable lesions because the dimensions of such lesions are difficult to measure accurately.

The response duration was calculated from the day of the first sign of a response until disease progression; time-to-progression (TTP) was calculated from the date of study entry until documented disease progression; 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 the median TTP were estimated using the Kaplan–Meier method. Compliance was calculated for all treatment courses using the ratio of the total dose actually administered to the scheduled dose.

Physical examinations, complete blood cell counts, biochemistry tests, and urinalyses were performed at least biweekly. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Objective responses and adverse events were confirmed by an external review committee.

Analysis was to be performed when 19 patients were enrolled. In this study, the threshold rate was defined as 5% and the expected rate was set as 15%. If the lower limit of the 90% confidence interval exceeded the 5% threshold (objective response in four or more of the 19 patients), S-1 was judged to be effective and we would proceed to the next large-scale study. If the upper limit of the 90% confidence interval did not exceed the expected rate of 15% (no objective response in the 19 patients), S-1 was judged to be ineffective and the study was to be ended. If response was confirmed in 1–3 of the 19 patients, whether to proceed to the next study or not was judged based on the safety and survival data from the present study.

Pharmacokinetics

A pharmacokinetic study was performed in the first eight patients enrolled in the study. Blood (5 ml) was collected before and 1, 2, 4, 6, 8, 10, and 12 h after the administration of S-1 on day 1 of the first course. The plasma was then separated by centrifugation and stored at −20°C until analysis. Plasma concentrations of FT were quantified using high-performance liquid chromatography with UV detection, and the concentrations of 5-FU, CDHP, and Oxo were quantified using gas chromatography-negative ion chemical ionisation mass spectrometry, as reported previously (Matsushima *et al*, 1997).

Pharmacokinetic parameters, including the maximum plasma concentration (C_{max}, ng ml^{-1}), time to reach C_{max} (T_{max}, h), area under the concentration *vs* time curve for zero to infinity ($AUC_{0-\infty}$, ng h ml^{-1}), and the elimination half-life ($T_{1/2}$, h) were calculated using a noncompartment model and Win-Nonlin software, Version 3.1 (Pharsight, Apex, NC, USA).

RESULTS

Patients

Nineteen consecutive eligible patients with advanced biliary tract cancer were enrolled in the study between July 2000 and January 2002 at the National Cancer Center Hospital, Tokyo, Japan. The patient characteristics are summarised in Table 1. Before the start of the study, six patients had received surgical resection and seven patients had undergone percutaneous or endoscopic biliary drainage for obstructive jaundice. Of the 19 patients, 17 had metastatic disease at the time of their enrollment in the study, while two patients were diagnosed as having locally advanced disease. The liver was the most common site of metastases (14 patients), followed by the distant lymph nodes (11 patients) and the lungs (three patients).

Treatments

In all, 19 patients were given a total of 63 courses of chemotherapy, with a median of two courses each (range, 1–12). The initial administered dose of S-1 was 100 mg day^{-1} in seven patients and 120 mg day^{-1} in 12 patients. Dose reduction was required in one patient because of grade 2 diarrhoea after the third course of treatment. The reasons for treatment discontinuation were as follows: disease progression (16 patients), grade 3 diarrhoea and

Table 1 Patient characteristics ($n = 19$)

Characteristics		No. of patients (%)
Gender		
Male		12 (63.2)
Female		7 (36.8)
Median age (years) (range)	59 (44–71)	
Karnofsky performance status, points		
100		8 (42.1)
90		10 (52.6)
80		1 (5.3)
Median body surface area (m^2) (range)	1.56 (1.37–1.83)	
Median first dose ($mg\,m^{-2}\,day^{-1}$) (range)	72.9 (65.8–78.6)	
History of surgical resection		6 (31.6)
Primary tumour site		
Gallbladder		16 (84.2)
Extrahepatic bile ducts		2 (10.5)
Ampulla of Vater		1 (5.3)
Median CEA ($ng\,ml^{-1}$) (range)	6.8 (1–737)	
Median CA 19-9 ($U\,ml^{-1}$) (range)	103 (1–48,160)	

Table 2 Response results ($n = 19$)

	Total	CR	PR	NC	PD	NE	Response rate (%)
Overall	19	0	4	9	5	1	21.1
Primary tumour site							
Gallbladder	16	0	3	8	4	1	18.8
Extrahepatic bile ducts	2	0	0	1	1	0	0
Ampulla of Vater	1	0	1	0	0	0	100.0

CR = Complete response; PR = partial response; NC = no change; PD = progressive disease; NE = not evaluable.

grade 3 stomatitis (one patient), prolonged grade 2 nausea (one patient), and patient's request for transference to another hospital (one patient). Except for two patients, in whom treatment was abandoned because of toxicities, all the patients were treated as outpatients. The overall compliance rate was 94.3%.

Response and survival

Of the 19 patients, none of the patients showed a CR but four patients achieved a PR, giving an overall response rate of 21.1% (95% confidence interval, 6.1–45.6%) (Table 2). The median response duration was 6.7 months (range, 2.8–10.0 months). Nine patients showed NC and five patients had PD. The tumour response could not be evaluated in one patient because the patient was transferred to another hospital, for personal reasons, prior to the response evaluation. At the time of analysis, 18 of the 19 patients had died because of disease progression. The median TTP was 3.7 months, and the overall median survival time was 8.3 months, with a 1-year survival rate of 21.1% (Figure 1).

Toxicity

All 19 patients were assessed for toxicities that are listed in Table 3. Treatment was generally well tolerated throughout the study. Although haematologic and gastrointestinal toxicities were common, most of the toxicities were mild and transient. Grade 3 anorexia and fatigue occurred in two patients each (10.5%), and grade 3 anaemia, neutropenia, stomatitis, nausea, diarrhoea, and fever occurred in one patient each (5.3%). No signs of cumulative

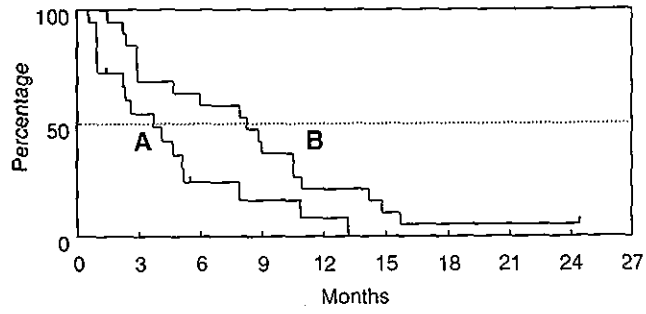

Figure 1 Time to progression (**A**) and overall survival time (**B**).

Table 3 Treatment-related adverse events ($n = 19$): worst grade reported during treatment period

	Grade[a]					
Toxicity	1	2	3	4	Grade 1–4 (%)	Grade 3–4 (%)
Haematologic						
Leukopenia	5	3	0	0	42.1	0
Neutropenia	4	2	1	0	36.8	5.3
Anaemia	3	4	1	0	42.1	5.3
Thrombocytopenia	2	0	0	0	10.5	0
Nonhaematologic						
Nausea	4	2	1	0	36.8	5.3
Vomiting	4	0	0	0	21.1	0
Anorexia	3	0	2	0	26.3	10.5
Stomatitis	3	0	1	0	21.1	5.3
Diarrhoea	2	2	1	0	26.3	5.3
Total bilirubin	1	1	0	0	10.5	0
ALT	2	4	0	0	31.6	0
AST	4	2	0	0	31.6	0
Fatigue	0	0	2	0	10.5	10.5
Fever	0	0	1	0	5.3	5.3
Rash	1	0	0	0	5.3	0
Pigmentation changes	3	0	0	0	15.8	0

AST = aspartate aminotransferase; ALT = alanine aminotransferase. [a]NCI Common Toxicity Criteria, version 2.0.

toxicity were noted. Of the 17 patients who were treated as outpatients, one patient required hospitalisation because of grade 3 nausea, anorexia, and fatigue during the middle of the first course of treatment. Although one patient died within 8 weeks of study enrollment because of rapid disease progression, no treatment-related deaths were observed.

Pharmacokinetics

Table 4 and Figure 2 show the results of the pharmacokinetic study for S-1 in the current study. The pharmacokinetic parameters for S-1 in other cancers, as reported by Hirata *et al* (1999) are also shown in Table 4 and Figure 2 for reference. Hirata *et al* investigated the pharmacokinetic parameters after the single administration of S-1 at a dose of $40\,mg\,m^{-2}$ in 12 Japanese patients with gastric, colorectal, and breast cancer. The parameters of 5-FU in both studies were similar, and no large differences in the parameters of other compounds, including CDHP, were seen.

DISCUSSION

Although most patients with biliary tract cancer have an unresectable disease at the time of diagnosis, no standard chemotherapies have been established for this disease (Hejna

Table 4 Pharmacokinetic parameters after single administration of S-1 at a dose of 40 mg m^{-2}

Compound	Parameter	Current study ($n=8$)	Hirata's study ($n=12$)
FT	C_{max} (ng ml^{-1})	1721.6±400.4	1971.0±269.0
	T_{max} (h)	3.6±1.1	2.4±1.2
	AUC (ng h ml^{-1})	24643.0±7915.0[a]	28216.9±7771.4[b]
	$T_{1/2}$ (h)	8.2±2.0	13.1±3.1
5-FU	C_{max} (ng ml^{-1})	146.9±62.1	128.5±41.5
	T_{max} (h)	4.0±0.0	3.5±1.7
	AUC (ng h ml^{-1})	799.8±285.3[a]	723.9±272.7[c]
	$T_{1/2}$ (h)	1.9±0.3	1.9±0.4
CDHP	C_{max} (ng ml^{-1})	245.3±64.9	284.6±116.6
	T_{max} (h)	3.3±1.0	2.1±1.2
	AUC (ng h ml^{-1})	1472.6±381.6[a]	1372.2±573.7[b]
	$T_{1/2}$ (h)	3.2±0.7	3.0±0.5
Oxo	C_{max} (ng ml^{-1})	55.3±48.4	78.0±58.2
	T_{max} (h)	3.3±1.0	2.3±1.1
	AUC (ng h ml^{-1})	230.6±140.2[a]	365.7±248.6[d]
	$T_{1/2}$ (h)	2.8±0.6	3.0±1.4

Parameters are represented as mean±s.d. [a]$AUC_{0-\infty}$. [b]AUC_{0-48}. [c]AUC_{0-14}. [d]AUC_{0-24}. FT = tegafur; 5-FU = 5-fluorouracil; CDHP = 5-chloro-2,4-dihydroxypyridine; Oxo = oteracil potassium.

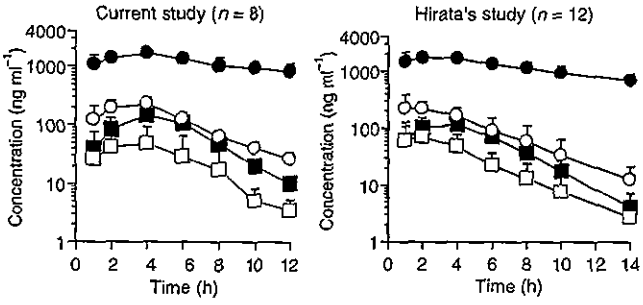

Figure 2 Plasma concentration–time profiles of FT (●), 5-FU (■), CDHP (○), and Oxo (□) after administration of S-1. The values are expressed as the mean ± s.d.

et al, 1998; van Riel *et al*, 1999; Okusaka, 2002; Yee *et al*, 2002). Since biliary tract cancer is an uncommon disease, studies of chemotherapy for biliary tract cancer are relatively few, and the number of included patients is generally small. In addition, the response rates and survival times described in published studies are difficult to compare because most studies contain patients with heterogeneous tumour groups, such as intrahepatic or extrahepatic bile duct cancer and gallbladder cancer. 5-fluorouracil has been the most commonly studied drug for this disease, although the antitumour effect of single-agent 5-FU is limited, with a response rate of less than 20%. Although the combined use of 5-FU with other agents, such as leucovorin, mitomycin C, or cisplatin, often produces a response rate of over 20% (Polyzos *et al*, 1996; Ducreux *et al*, 1998; Taïeb *et al*, 2002), the toxicities also become greater; whether combination therapies contribute to prolonged survival remains uncertain. In recent small-scale studies, gemcitabine has shown relatively good response rates, ranging from 8 to 36%, for biliary tract cancer (Mezger *et al*, 1998; Raderer *et al*, 1999; Gallardo *et al*, 2001; Gebbia *et al*, 2001; Kubicka *et al*, 2001; Penz *et al*, 2001; Tsavaris *et al*, 2004), but large-scale studies are needed to confirm its efficacy. Therefore, the development of new effective chemotherapeutic agents is urgently needed to improve survival in patients with advanced biliary tract cancers.

A novel orally administered drug, S-1, has been developed based on the biochemical modulations by CDHP, a dihydropyrimidine dehydrogenase inhibitor, and Oxo, a protector against 5-FU-induced gastrointestinal toxicity; S-1 has exhibited significant antitumour effects on various solid cancers (Sakata *et al*, 1998; Koizumi *et al*, 2000; Ohtsu *et al*, 2000; Inuyama *et al*, 2001; Kawahara *et al*, 2001; Chollet *et al*, 2003; Van den Brande *et al*, 2003). Since the drug is available in oral form, S-1 has a potential advantage, as far as patient convenience is concerned, especially in terms of quality-of-life. This consideration is very important for biliary tract cancer patients because their remaining lifespan is generally short. Consequently, the efficacy of S-1 for the treatment of biliary tract cancer was examined.

In the current study, S-1 produced a good response rate of 21.1%, which is superior to those obtained with other single agents, including 5-FU, mitomycin C, and cisplatin (Table 5), suggesting an antitumour effect of S-1 on biliary tract cancer. In this study, patients with gallbladder cancer accounted for three of the four responders; however, the efficacy of S-1 for each primary tumour site cannot be accurately assessed because of the small number of subjects analysed.

Table 5 Recent studies of single-agent chemotherapy for biliary tract cancer

Author	Regimen	No. of patients: Total	No. of patients: Gallbladder Ca.	Response rate (%)	MST (months)
Takada *et al* (1994)	5-FU	18	10	0	NA
Taal *et al* (1993)	Mitomycin C	30	13	10	4.5
Okada *et al* (1994)	Cisplatin	13	6	8	5.5
Jones *et al* (1996)	Paclitaxel	15	4	0	NA
Pazdur *et al* (1999)	Docetaxel	17	0	0	NA
Papakostas *et al* (2001)	Docetaxel	25	16	20	8
Sanz-Altamira *et al* (2001)	Irinotecan	25	10	8	10
Mezger *et al* (1998)	Gemcitabine	13	4	8	NA
Raderer *et al* (1999)	Gemcitabine	19	5	16	6.5
Penz *et al* (2001)	Gemcitabine[a]	32	10	22	11.5
Kubicka *et al* (2001)	Gemcitabine	23	0	30	9.3
Gallardo *et al* (2001)	Gemcitabine	26	26	36	7
Gebbia *et al* (2001)	Gemcitabine	18	12	22	8
Tsavaris *et al* (2004)	Gemcitabine	30	14	30	14
Current study	S-1	19	16	21	8.3

5-FU: 5-fluorouracil; MST: median survival time; NA: not available. [a]Biweekly.

Since patients with biliary tract cancer tend to suffer various tumour-related complications, such as cholangitis and impaired liver function, enhanced chemotherapy-related toxicities, including neutropenic sepsis, are a concern. However, S-1 was well tolerated in the present study, and no grade 4 toxicities occurred. Haematological toxicities were acceptable and similar to the results of clinical studies examining S-1 for the treatment of other cancers in Japan. Gastrointestinal toxicities were also well tolerated, as in the other Japanese studies, although strong gastrointestinal toxicities, particularly severe diarrhoea, have been reported in Western countries (van Groeningen *et al*, 2000; Cohen *et al*, 2002; Chollet *et al*, 2003; Van den Brande *et al*, 2003). The difference in toxicities between the Japanese and Western studies remains unexplained, although the conversion of FT to 5-FU seems to occur more slowly in Japanese patients than in patients from other ethnic groups (Comets *et al*, 2003). A pharmacokinetic study suggested that the pharmacokinetic parameters of S-1 were similar in patients with biliary tract cancer and in patients with other cancers in Japan.

Since no serious adverse events occurred in this study, most of the patients were treated as outpatients, enabling a relatively good quality-of-life. The S-1 compliance rate of the patients was very good (94.3%), with only one patient requiring a dose reduction and only two patients discontinuing S-1 because of toxicity. In view of the favourable toxicity profile, its evaluation in combination with other agents might be of particular interest to improve therapeutic results. Combination therapy with S-1 and cisplatin has already been conducted for gastric cancer, and an excellent response rate of 76% was reported in a phase II study (Ohtsu *et al*, 2001).

In conclusion, the results of this study indicate that S-1 is a safe and active agent for the treatment of patients with biliary tract cancer. Further investigations of this agent are warranted in this population of patients with a poor prognosis.

Clinical

ACKNOWLEDGEMENTS

We thank Drs S Okada, M Kurihara, S Matsuno, O Ishikawa, and T Taguchi for their kind advice; Drs H Saisho, N Moriyama, and W Koizumi for performing the extramural review; and Misses T Tomizawa and Y Kawaguchi for their support. We also thank Messrs T Tahara, T Tsuruda, A Fukushima, M Noguchi, and Dr R Azuma for their assistance with the data management and Mr K Kuwata for performing the pharmacokinetic analysis. This work was supported by Taiho Pharmaceutical Co. Ltd, Tokyo, Japan.

REFERENCES

Chollet P, Schoffski P, Weigang-Kohler K, Schellens JH, Cure H, Pavlidis N, Grunwald V, De Boer R, Wanders J, Fumoleau P (2003) Phase II trial with S-1 in chemotherapy-naive patients with gastric cancer. A trial performed by the EORTC Early Clinical Studies Group (ECSG). *Eur J Cancer* 39: 1264–1270

Cohen SJ, Leichman CG, Yeslow G, Beard M, Proefrock A, Roedig B, Damle B, Letrent SP, DeCillis AP, Meropol NJ (2002) Phase I and pharmacokinetic study of once daily oral administration of S-1 in patients with advanced cancer. *Clin Cancer Res* 8: 2116–2122

Comets E, Ikeda K, Hoff P, Fumoleau P, Wanders J, Tanigawara Y (2003) Comparison of the pharmacokinetics of S-1, an oral anticancer agent, in Western and Japanese patients. *J Pharmacokinet Pharmacodyn* 30: 257–283

Ducreux M, Rougier P, Fandi A, Clavero-Fabri MC, Villing AL, Fassone F, Fandi L, Zarba J, Armand JP (1998) Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. *Ann Oncol* 9: 653–656

Gallardo JO, Rubio B, Fodor M, Orlandi L, Yanez M, Gamargo C, Ahumada M (2001) A phase II study of gemcitabine in gallbladder carcinoma. *Ann Oncol* 12: 1403–1406

Gebbia V, Giuliani F, Maiello E, Colucci G, Verderame F, Borsellino N, Mauceri G, Caruso M, Tirrito ML, Valdesi M (2001) Treatment of inoperable and/or metastatic biliary tree carcinomas with single-agent gemcitabine or in combination with levofolinic acid and infusional fluorouracil: results of a multicenter phase II study. *J Clin Oncol* 19: 4089–4091

Hejna M, Pruckmayer M, Raderer M (1998) The role of chemotherapy and radiation in the management of biliary cancer: a review of the literature. *Eur J Cancer* 34: 977–986

Hirata K, Horikoshi N, Aiba K, Okazaki M, Denno R, Sasaki K, Nakano Y, Ishizuka H, Yamada Y, Uno S, Taguchi T, Shirasaka T (1999) Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. *Clin Cancer Res* 5: 2000–2005

Inuyama Y, Kida A, Tsukuda M, Kohno N, Satake B (2001) Late phase II study of S-1 in patients with advanced head and neck cancer. *Gan To Kagaku Ryoho* 28: 1381–1390

Japan Society for Cancer Therapy (1993) Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. *J Jpn Soc Cancer Ther* 28: 101–130

Jones Jr DV, Lozano R, Hoque A, Markowitz A, Patt YZ (1996) Phase II study of paclitaxel therapy for unresectable biliary tree carcinomas. *J Clin Oncol* 14: 2306–2310

Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S, Hasegawa K, Niitani H (2001) Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* 85: 939–943

Koizumi W, Kurihara M, Nakano S, Hasegawa K (2000) Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. *Oncology* 58: 191–197

Kubicka S, Rudolph KL, Tietze MK, Lorenz M, Manns M (2001) Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. *Hepatogastroenterology* 48: 783–789

Matsushima E, Yoshida K, Kitamura R (1997) Determination of S-1 (combined drug of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate) and 5-fluorouracil in human plasma and urine using high-performance liquid chromatography and gas chromatography-negative ion chemical ionization mass spectrometry. *J Chromatogr B Biomed Sci Appl* 691: 95–104

Mezger J, Sauerbruch T, Ko Y, Wolter H, Funk C, Glasmacher A (1998) Phase II study of gemcitabine in gallbladder and biliary tract carcinomas. *Onkologie* 21: 232–234

Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K, Taguchi T (2000) Phase II study of S-1, a novel oral fluorophyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 Cooperative Colorectal Carcinoma Study Group. *Br J Cancer* 83: 141–145

Ohtsu A, Boku N, Nagashima F, Koizumi W, Tanabe S, Saigenji K, Muro K, Matsumura Y, Shirao K (2001) A phase I/II study of S-1 plus cisplatin (CDDP) in patients (pts) with advanced gastric cancer (AGC). *Proc Am Soc Clin Oncol* 20: 656

Okada S, Ishii H, Nose H, Yoshimori M, Okusaka T, Aoki K, Iwasaki M, Furuse J, Yoshino M (1994) A phase II study of cisplatin in patients with biliary tract carcinoma. *Oncology* 51: 515–517

Okada S, Okusaka T, Ueno H, Ikeda M, Kuriyama H, Saisho T, Morizane C (2002) A phase II and pharmacokinetic trial of S-1 in patients with advanced pancreatic cancer (APC). *Proc Am Soc Clin Oncol* 22: 171a

Okusaka T (2002) Chemotherapy for biliary tract cancer in Japan. *Semin Oncol* 29: 51–53

Papakostas P, Kouroussis C, Androulakis N, Samelis G, Aravantinos G, Kalbakis K, Sarra E, Souglakos J, Kakolyris S, Georgoulias V (2001) First-line chemotherapy with docetaxel for unresectable or metastatic carcinoma of the biliary tract. A multicentre phase II study. *Eur J Cancer* 37: 1833–1838

Pazdur R, Royce ME, Rodriguez GI, Rinaldi DA, Patt YZ, Hoff PM, Burris HA (1999) Phase II trial of docetaxel for cholangiocarcinoma. *Am J Clin Oncol* 22: 78–81

Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, Depisch D, Krauss G, Schneeweiss B, Scheithauer W (2001) Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. *Ann Oncol* 12: 183–186

Polyzos A, Nikou G, Giannopoulos A, Toskas A, Kalahanis N, Papargyriou J, Michail P, Papachristodoulou A (1996) Chemotherapy of biliary tract cancer with mitomycin-C and 5-fluorouracil biologically modulated by folinic acid. *A phase II study. Ann Oncol* 7: 644–645

Raderer M, Hejna MH, Valencak J B, Kornek GV, Weinlander GS, Bareck E, Lenauer J, Brodowicz T, Lang F, Scheithauer W (1999) Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. *Oncology* 56: 177–180

Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T (1998) Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 34: 1715–1720

Sanz-Altamira PM, O'Reilly E, Stuart KE, Raeburn L, Steger C, Kemeny NE, Saltz LB (2001) A phase II trial of irinotecan (CPT-11) for unresectable biliary tree carcinoma. *Ann Oncol* 12: 501–504

Shirasaka T, Nakano K, Takechi T, Satake H, Uchida J, Fujioka A, Saito H, Okabe H, Oyama K, Takeda S, Unemi N, Fukushima M (1996b) Antitumor activity of 1 M tegafur–0.4 M 5-chloro-2,4-dihydroxypyridine–1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res* 56: 2602–2606

Shirasaka T, Shimamoto Y, Fukushima M (1993) Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 53: 4004–4009

Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, Fukushima M (1996a) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 7: 548–557

Taal BG, Audisio RA, Bleiberg H, Blijham GH, Neijt JP, Veenhof CH, Duez N, Sahmoud T (1993) Phase II trial of mitomycin C (MMC) in advanced gallbladder and biliary tree carcinoma. An EORTC Gastrointestinal Tract Cancer Cooperative Group Study. *Ann Oncol* 4: 607–609

Taïeb J, Mitry E, Boige V, Artru P, Ezenfis J, Lecomte T, Clavero-Fabri MC, Vaillant JN, Rougier P, Ducreux M (2002) Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma. *Ann Oncol* 13: 1192–1196

Takada T, Kato H, Matsushiro T, Nimura Y, Nagakawa T, Nakayama T (1994) Comparison of 5-fluorouracil, doxorubicin and mitomycin C with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinomas. *Oncology* 51: 396–400

Tatsumi K, Fukushima M, Shirasaka T, Fujii S (1987) Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res* 78: 748–755

Tsavaris N, Kosmas C, Gouveris P, Gennatas K, Polyzos A, Mouratidou D, Tsipras H, Margaris H, Papastratis G, Tzima E, Papadoniou N, Karatzas G, Papalambros E (2004) Weekly gemcitabine for the treatment of biliary tract and gallbladder cancer. *Invest New Drugs* 22: 193–198

Van den Brande J, Schoffski P, Schellens JH, Roth AD, Duffaud F, Weigang-Kohler K, Reinke F, Wanders J, de Boer RF, Vermorken JB, Fumoleau P (2003) EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. *Br J Cancer* 88: 648–653

van Groeningen CJ, Peters GJ, Schornagel JH, Gall H, Noordhuis P, de Vries MJ, Turner SL, Swart MS, Pinedo HM, Hanauske AR, Giaccone G (2000) Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. *J Clin Oncol* 18: 2772–2779

van Riel JM, van Groeningen CJ, Pinedo HM, Giaccone G (1999) Current chemotherapeutic possibilities in pancreaticobiliary cancer. *Ann Oncol* 10: 157–161

Yee K, Sheppard BC, Domreis J, Blanke CD (2002) Cancers of the gallbladder and biliary ducts. *Oncology (Huntingt)* 16: 939–957