Table 1. Baseline characteristics and demographics (n = 106)

Characteristic	
Median age (range) (years)	62 (36–78)
Gender, *n* (%)	
Male	56 (52.8)
Female	50 (47.2)
Median bodyweight (range) (kg)	52.3 (33.1–95.0)
Smoking history,† *n* (%)	
Never smoker	39 (36.8)
Past smoker	37 (34.9)
Current smoker	30 (28.3)
ECOG PS, *n* (%)	
0	80 (75.5)
1	26 (24.5)
2	0 (0)
Disease status, *n* (%)	
Metastatic	88 (83.0)
Locally advanced	18 (17.0)
Primary tumor identified, *n* (%)	92 (86.8)
Primary sites, *n* (%)	
Head	46 (43.4)
Body and tail	23 (21.7)
Body	22 (20.8)
Tail	10 (9.4)
Other	5 (4.7)‡
Biliary drainage, *n* (%)	19 (17.9)
Sites of distant metastases, *n* (%)	
Liver	56 (52.8)
Distant lymph nodes	39 (36.8)
Lung	17 (16.0)
Other	26 (24.5)
Prior lines of therapy, *n* (%)	
None	101 (95.3)
One regimen	5 (4.7)§
Median CA19–9 (range) (U/mL)	
Median	776 (0–435 000)
Median CEA (range) (ng/mL)	
Median	4.8 (0.6–1100.1)

†Never smoker, never/hardly smoked; past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). ‡Whole of pancreas (n = 1); head and body (n = 3); other (n = 1). §Tegafur, gimeracil, oteracil potassium (S-1) (n = 3); 5-fluorouracil plus leucovorin (n = 2). CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Co-Operative Group.

93.4% of the patients; most cases were mild to moderate in severity (87.7%, grade ≤2; 5.7%, grade ≥3). Other common non-hematological AE included anorexia, pruritus, fatigue, nausea and diarrhea. Most patients experienced some degree of hematological toxicity, with grade 3 or 4 neutropenia (neutrophil decreased), leucopenia (white blood cell count decreased) and anemia (hemoglobin decreased) occurring in 34.9%, 29.2% and 14.2% of patients, respectively. Only one treatment-related death occurred (due to gastrointestinal hemorrhage), which was probably due to arterial bleeding caused by the invasion of the primary tumor into the gastrointestinal tract. Although the likelihood of this event being treatment-related was deemed remote, a causal relationship could not be completely excluded because the event occurred during the study treatment administration period.

Treatment-related SAE were reported in 26 (24.5%) patients. These included nine ILD-like events (8.5%), the majority of which (n = 7) were grade 1–2 in severity. Importantly, all of these nine patients recovered or improved, and four of these patients did so without any treatment for ILD-like events. Other

Table 2. Treatment-related adverse events occurring in >30% of patients treated with erlotinib and gemcitabine (n = 106)

	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Non-hematological			
Rash	78 (73.6)	3 (2.8)	0 (0)
Anorexia	75 (70.8)	15 (14.2)	0 (0)
Pruritus	57 (53.8)	1 (0.9)	0 (0)
Fatigue	56 (52.8)	3 (2.8)	0 (0)
Nausea	56 (52.8)	6 (5.7)	0 (0)
Diarrhea	52 (49.1)	2 (1.9)	0 (0)
Dry skin	49 (46.2)	0 (0)	0 (0)
Stomatitis	38 (35.8)	0 (0)	0 (0)
Pyrexia	32 (30.2)	0 (0)	0 (0)
Hematological			
White blood cell count decreased	85 (80.2)	31 (29.2)	0 (0)
Platelet count decreased	77 (72.6)	9 (8.5)	0 (0)
Hemoglobin decreased	76 (71.7)	13 (12.3)	2 (1.9)
Hematocrit decreased	73 (68.9)	8 (7.5)	0 (0)
Neutrophil decreased	73 (68.9)	32 (30.2)	5 (4.7)
Red blood cell count decreased	72 (67.9)	8 (7.5)	0 (0)
ALT increased	59 (55.7)	10 (9.4)	0 (0)
AST increased	57 (53.8)	4 (3.8)	1 (0.9)
Weight decreased	53 (50.0)	3 (2.8)	0 (0)
Lymphocyte count decreased	46 (43.4)	14 (13.2)	0 (0)
Blood albumin decreased	35 (33.0)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	35 (33.0)	12 (11.3)	1 (0.9)

ALT, alanine amino transferase; AST, aspartate amino transferase.

treatment-related SAE were anorexia (3.8%), vomiting, pyrexia and abnormal hepatic function (1.9% each). The baseline characteristics, treatment and outcomes of patients who developed treatment-related ILD-like events during the study are detailed in Table 3. The onset times of ILD-like events ranged from 7 to 187 days after the start of treatment. In these patients, a relatively long survival was observed (from 119 to 568+ days), and five patients received post-study therapy. All of these nine patients were past or current smokers, and six had emphysema at baseline (not detected prior to treatment, but diagnosed at the extramural review by a radiologist in the DSMC). Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model and emphysema at baseline was indicated as a risk factor for onset of ILD-like events (odds ratio [95% CI], 12.13 [1.01–145.7]; P = 0.0491).

Adverse events led to erlotinib discontinuation in 30 patients (28.3%) and gemcitabine discontinuation in 27 patients (25.5%). The main reasons for treatment discontinuation were ILD (n = 6) and anorexia (n = 3); no patient discontinued treatment due to RASH or diarrhea. Due to the onset of AE, a total of 65 patients (61.3%) required one or more interruptions of erlotinib (36 patients [34.0%] for longer than seven consecutive days and 17 patients [16.0%] for longer than 14 consecutive days) and 56 patients (52.8%) had one or more skip of gemcitabine. Modifications in the erlotinib or gemcitabine dosage were required in 17 (16.0%) and 11 (10.4%) patients, respectively, due to AE.

Efficacy. The median OS was 9.23 months (95% CI, 8.31–10.78; Fig. 1A) and the 1-year survival rate was 33% (95% CI, 24–42). Median PFS was 3.48 months (95% CI, 2.63–3.78; Fig. 1B). Among the patients evaluable for tumor response (n = 64), the ORR was 20.3% (13/64; 95% CI, 11.3–32.2) and the DCR was 50.0% (95% CI, 37.2–62.8; CR, n = 0; PR, n = 13; stable disease, n = 19).

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Table 3. Characteristics, treatment and outcomes of patients with treatment-related ILD-like events (n = 9)

Event	Gender	Age (years)	Smoking status†	Days on treatment	ILD maximum grade	Suspicious findings of ILD	Steroids	Oxygen	ILD outcome	Presence of emphysema (assessed by radiologist)	Survival outcome (days)	Post-therapy (chemotherapy)
Lymphoid ILD	M	62	Past	82	1	Pyrexia	None	No	Improved	Yes	362	Yes
ILD	M	42	Current	50	3	Pyrexia	Pulse	Yes	Recovered	Yes	517	Yes
Organising pneumonia	M	60	Past	183	2	Respiratory symptoms	None	No	Improved	Yes	568+	Yes
ILD	F	62	Past	113	2	Cough	Oral	No	Recovered	Yes	376	No
ILD	F	74	Past	111	3	Cough, dyspnea	Pulse	Yes	Improved	None	183	No
ILD	M	60	Current	25	1	Pyrexia	Pulse	No	Recovered	None	119	Yes
ILD	M	77	Past	7	1	X-ray	None	No	Recovered	Yes	255	No
ILD	M	55	Past	187	1	CT	None	No	Recovered	Yes	415	No
ILD	F	60	Current	76	2	Cough	Oral	No	Recovered	None	346	Yes

†Past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). CT, computed tomography; F, female; ILD, interstitial lung disease; M, male.

The median OS was longer in patients who experienced RASH of grade ≥2 (n = 67) than in those with RASH of grade ≤1 (n = 39) (10.25 months [95% CI, 8.80–12.12] *vs* 8.31 months [95% CI, 6.18–9.99], respectively; Fig. 1C) and the 1-year survival rate was higher (39% [95% CI, 27–50] *vs* 23% [95% CI, 10–36], respectively). Similarly, the median PFS was longer in patients with RASH of grade ≥2 versus those with RASH grade ≤1 (3.61 months [95% CI, 3.48–5.32] *vs* 1.81 months [95% CI, 1.64–3.48]; Fig. 1D). While there was no notable difference in ORR between patients with RASH grade ≥2 and those with grade ≤1 (21.1% [95% CI, 9.6–37.3] *vs* 19.2% [95% CI, 6.6–39.4]), the DCR was higher in those with more severe RASH (60.5% [95% CI, 43.4–76.0] *vs* 34.6% [95% CI, 17.2–55.7]).

Pharmacokinetics. Plasma sampling for PK analyses was performed in all six patients enrolled in the first step. On day 8, the values of C_{max} were 1760 ± 456.9 ng/mL (mean ± SD) for erlotinib, 169.7 ± 64.5 ng/mL for OSI-420 and 22 700 ± 3272.9 ng/mL for gemcitabine. The AUC_{last} was 29 001 ± 6560 h ng/mL, 2748 ± 788 h ng/mL and 10 717 ± 1458 h ng/mL (mean ± SD), respectively. The mean t_{max} was 8.0 h (range, 2.0–23.9 h), 9.0 h (2.0–23.9 h) and 0.51 h (0.45–0.57 h), respectively. Also on day 8, the mean plasma $t_{1/2}$ was 54.92 h (range, 9.25–144.61 h), 32.79 h (10.36–60.46 h), and 0.63 h (0.31–1.14 h), respectively. The Cl/F of erlotinib and gemcitabine showed interindividual variability; the Cl/F on day 8 was 3972.6 ± 772.1 mL/h (mean ± SD; coefficient of variation 19.4%) and 146 580.4 ± 31 101.3 mL/h (21.2%), respectively.

Biomarker analysis. Of the 106 patients enrolled, *EGFR* mutation status was evaluated in 47 patients (44.3%), all of whom had wild-type *EGFR*. The mutation status of the remaining patients was classified as unknown because samples were not available (30.2%), not examined (9.4%) or the results following sequencing were inconclusive (16.0%).

Discussion

This study was designed to initially assess the safety of erlotinib with gemcitabine for Japanese patients with pancreatic cancer, in whom there had been no prior exposure to either drug. As no significant safety concerns were raised in the first step of the study, enrollment of a further 101 patients was performed. Although the incidence of AE in this study was higher than in the PA.3 study, the incidence of grade 3–4 AE was similar.[28] Despite these results, no new AE specific to Japanese patients were observed. As expected, RASH and gastrointestinal events were among the most common AE in this study, and most of these cases were mild to moderate in severity.

Interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%) in the current study, while its incidence was reported to be 2.4% in patients treated in the erlotinib plus gemcitabine arm of the PA.3 study.[28] In addition, in Japanese patients with advanced pancreatic cancer, ILD-like events were reported in two (6.1%) of 33 patients treated with gemcitabine plus S-1, and were reported in three (1.1%) of 264 patients with gemcitabine monotherapy, respectively.[33,34] Likewise, the higher incidence of ILD-like events were documented using S-1 or erlotinib in combination with gemcitabine compared with gemcitabine as monotherapy in patients with pancreatic and biliary tract cancer.[35] On another front, outside of Japan, a high incidence of ILD-like events was reported in gemcitabine and paclitaxel combination therapy in patients with NSCLC.[36] From the above information, considering the higher incidence of ILD when gemcitabine is used in combination, an additive effect from such combinations cannot be ruled out.

In NSCLC, Japanese patients have an increased risk of developing ILD-like events when treated with EGFR TKI.[29,37–39] Fatal cases of ILD-like events have been reported following EGFR TKI administration for the treatment of NSCLC.[37–41] Importantly, however, no patients died due to an ILD-like event in this study. Seven patients experienced ILD-like events of grade 1–2 in severity. This may be due to active management of ILD-like cases during the study period. This management included regular and immediate chest X-rays, in addition to diagnosis with CT scans after any early signs and symptoms were observed (e.g. pyrexia, cough or dyspnea), timely discontinuation of the antitumor drugs (as a precautionary measure in case these drugs were associated with the symptoms) and appropriate treatment for the events (including oral/pulse steroids). By appropriately treating the early symptoms of ILD-like events, patients could restart antitumor therapy (chemotherapy: treatment change). In this study, the onset time for ILD-like events varied markedly between patients (7–187 days). It is therefore necessary to monitor the patients throughout the treatment period.

All of the patients who developed ILD in this study were current or past smokers, and smoking status has been shown to be a risk factor for ILD in the NSCLC population.[38] Results from the multivariate analyses in this study suggest that emphysema is also a risk factor for developing ILD; six of the nine

patients with ILD-like events were diagnosed with emphysema at baseline. Although the number of reports of an ILD-like event may have been artificially elevated due to underlying patient baseline characteristics and the active management of ILD-like events, these results demonstrate the need to consider the risk of ILD-like events in Japanese patients treated with TKI. In particular, it is important that chest CT scans are closely checked for the presence of emphysema or comorbid ILD and that pulmonary status is assessed prior to treatment administration.

This study corroborates the results of the combination of gemcitabine and erlotinib shown in the PA.3 study. The median OS in this study of 9.23 months was longer than those reported in trials with gemcitabine alone. In this study, patients who experienced skin toxicity of grade ≥2 had better outcomes than those with less severe toxicity or the overall study population. Retrospective analyses of data from the PA.3 and AViTA studies have found a significant association between the development of skin toxicity and efficacy in patients with pancreatic cancer treated with erlotinib-based therapy, although the precise mechanisms for the association between skin toxicity and effectiveness are unknown.[28,41,42]

Although the presence of mutations in the tyrosine-kinase region of the *EGFR* gene appears to predict a better response to erlotinib in NSCLC,[43,44] this has not yet been evaluated in pancreatic cancer. *EGFR* mutations are very rare in patients with pancreatic cancer;[45–47] indeed in the present study, no *EGFR* mutations were detected. Further work is required to determine whether *EGFR* mutations can be used as predictive markers for improved survival in Japanese patients receiving erlotinib and gemcitabine as treatment for advanced pancreatic cancer.

In conclusion, the present study shows that erlotinib in combination with gemcitabine is generally well tolerated in Japanese patients with advanced pancreatic cancer. This combination is associated with efficacy and survival outcomes, and the results of this study are consistent with the findings of the global PA.3 study.

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Original Article

A Phase I/II Study of Combined Chemotherapy with Mitoxantrone and Uracil/Tegafur for Advanced Hepatocellular Carcinoma

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Objective: The aim was to determine the recommended dose of combined chemotherapy with mitoxantrone and uracil/tegafur (Phase I part) and to clarify its efficacy and safety in patients with advanced hepatocellular carcinoma at the recommended dose (Phase II part).
Methods: Patients eligible had histologically confirmed, chemo-naive advanced hepatocellular carcinoma and were amenable to established forms of treatment. The therapy consisted of mitoxantrone administered intravenously at one of three dosages (6, 8 and 10 mg/m^2/day) on day 1 and uracil/tegafur administered orally at 300 mg/m^2 from day 1 through day 21. The treatment was repeated every 4 weeks until evidence of tumor progression or unacceptable toxicity.
Results: A total of 25 patients were enrolled. In the Phase I part, dose-limiting toxicities occurred in all three patients, given mitoxantrone at the dosage of 10 mg/m^2/day, and the recommended mitoxantrone dosage was determined to be 8 mg/m^2/day. Among 19 patients administered the drug at the recommended dosage, 1 patient (5.3%) showed partial response, 8 patients (42.1%) showed stable disease and 10 patients (52.6%) showed progressive disease. The median survival and median progression-free survival were 8.4 and 2.5 months, respectively. The most common toxicities were Grade 3–4 leukopenia (63.2%) and neutropenia (68.4%).
Conclusions: Mitoxantrone at 8 mg/m^2 combined with uracil/tegafur at 300 mg/m^2/day was determined to be the recommended regimen. Although this regimen was generally well tolerated, it appeared to have little activity against advanced hepatocellular carcinoma. These findings do not support the use of this combination regimen in practice.

Key words: hepatocellular carcinoma – chemotherapy Phase I/II – mitoxantrone – uracil/tegafur

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most commonly occurring cancers worldwide (1,2). Surgical resection, liver transplantation and local ablation therapy, including radiofrequency ablation and ethanol injection, are considered as curative treatment for HCC (3). Transcatheter arterial chemoembolization (TACE) has been applied to patients with advanced incurable HCC (4,5). However, the majority of HCC patients develop recurrence or metastasis, regardless of the treatment modalities employed. Although patients with HCC at this advanced stage are generally treated by systemic therapy, the prognosis remains poor (6,7). Sorafenib

is an orally administered molecular-targeted drug that targets tumor cell proliferation and tumor angiogenesis by inhibiting the serine–threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors 1, 2 and 3 and platelet-derived growth factor receptor β. This drug was reported to confer an overall survival advantage, with manageable toxicity, in comparison with placebo in a Phase III trial, and it has been accepted worldwide as the first-line chemotherapy for advanced HCC (8). But the advantage is modest. There is urgent need to develop more effective regimens.

5-Fluorouracil (5-FU) has been widely used for the treatment of various gastrointestinal malignancies, including advanced HCC (9,10). A high level of efficacy can be expected when the drug is given as a continuous intravenous infusion (11). However, this would necessitate a permanent intravenous access. Uracil/tegafur (UFT) is an orally administered drug which is a mixture of uracil and tegafur at a molar ratio of 4:1. Tegafur is a prodrug of 5-FU that is hydroxylated and converted to 5-FU by hepatic microsomal enzymes, and uracil prevents the degradation of 5-FU by inhibiting the enzyme dihydropyrimidine dehydrogenase, which results in an increased level of 5-FU in the plasma and tumor tissues (12,13). UFT has been reported to be as effective as intravenous 5-FU for the treatment of malignancies (14,15) and to be effective for the treatment of advanced HCC (16,17).

The therapeutic usefulness of doxorubicin in patients with advanced HCC has also been widely explored since the 1970s. A randomized trial in which doxorubicin was compared with supportive care alone for advanced HCC showed a significant survival benefit in the doxorubicin arm. However, treatment with this drug has not been accepted as a standard chemotherapy because of the high rate of fatal complications reported (18). Mitoxantrone, another anthracycline, has shown similar antitumor activity to that of doxorubicin in both human tumor cell lines and animal models of leukemia and has fewer myelotoxic and cardiotoxic effects than doxorubicin (19). Clinical trials of mitoxantrone have also demonstrated moderate activity against HCC, with a low incidence rate of adverse effects (20,21).

Combination chemotherapeutic regimens composed of a fluoropyrimidine and an anthracycline antibiotic have been reported to show moderate efficacy against HCC with tolerable toxicity (22–24), but combined chemotherapy with UFT and mitoxantrone has not yet been examined. We conducted Phase I/II studies to determine the recommended dosage of the combination of UFT with mitoxantrone (UFM regimen) and to clarify the efficacy and safety when administered at the recommended dose in patients with advanced HCC.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility criteria for study enrolment were: (i) patients with histologically confirmed HCC, who were (ii) unsuitable for surgical resection, local ablation therapy or TACE, (iii) were ≥20 years old, (iv) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, (v) had adequate bone marrow function (white blood cell ≥3000 cells/mm^3, absolute neutrophil count ≥1500 cells/mm^3, platelet count ≥70 000 cells/mm^3 and hemoglobin ≥8.0 g/dl), renal function [serum creatinine concentration ≤upper limit of normal (ULN)] and hepatic function [serum albumin level ≥3.0 mg/dl, total bilirubin level ≤3.0 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤5.0 × ULN], (vi) had a life expectancy of at least 12 weeks and (vii) provided written informed consent from each patient.

The exclusion criteria were: clinically evident congestive heart failure, serious cardiac arrhythmia, active or symptomatic coronary artery disease or ischemia, clinically serious infection, seizure disorder requiring medication, prior malignancy (any cancer treated curatively was permitted), clinically evident brain or meningeal metastasis, and pregnant/lactating women. This protocol was approved by the Institutional Review Board for clinical investigation of the National Cancer Center, in conformity with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

Study Treatment

UFT was administered orally at the dose of 300 mg/m^2 per day in two divided doses for 21 consecutive days, followed by a rest period of 7 days (400 mg/body per day in patients with a body surface area of <1.50 m^2 and 500 mg/body/day in patients with a body surface area of ≥1.50 m^2). Mitoxantrone was given as a 60 min intravenous infusion on day 1. This cycle was repeated every 28 days. Patients continued to receive additional courses of this regimen until a cumulative dose of mitoxantrone of 100 mg/m^2, evidence of disease progression or the appearance of unacceptable toxicity.

Phase I Part

The objectives of the Phase I study were to investigate the frequency of dose-limiting toxicity (DLT) and to determine the recommended dose of mitoxantrone and UFT. The criteria of DLT included: Grade 4 leukopenia or neutropenia, Grade 3 neutropenia accompanied by fever (≥38°C) or infection (clinically or biologically confirmed), thrombocytopenia <25 000/mm^3 or necessity of transfusion, Grade 3 or 4 non-hematological toxicity (except nausea/vomiting, anorexia, fatigue and hyperglycemia), AST and ALT >10 times the ULN, suspension of UFT administration for over 3 successive weeks, or an over 6-week delay in the commencement of the next treatment cycle.

Three possible dosage levels of mitoxantrone (Level 1: 6 mg/m^2/day, Level 2: 8 mg/m^2/day and Level 3: 10 mg/m^2/day) were assigned for the Phase I part (Table 1). The first

Table 1. Dose-escalation schedules of mitoxantrone and uracil/tegafur

Dose level	Mitoxantrone (mg/m^2)	UFT (mg/m^2)	Number of patients enrolled
1	6	300	3
2	8	300	6
3	10	300	3

UFT, uracil/tegafur.

patient to enter the study was started at Level 1. At least three patients were treated at this level and observed for DLT. Dose escalation was continued until at least one-third of the patients in a given cohort showed DLT. If none of the first three treated patients developed DLT during the first cycle at a specific dose level, the dose escalation was continued. If one of the first three treated patients developed DLT at any dose level, three additional patients were entered at the same dose level; if only one or two of six patients at a given level experienced a DLT, the dose escalation was continued. The maximum tolerated dose (MTD) was defined as the dose level at which one-third or more of the patients experienced a DLT. The recommended dose for the Phase II study was defined as the dose level preceding the attainment of the MTD.

Phase II Part

The primary endpoint of the Phase II part was the objective response rate. The secondary endpoints were the overall survival, progression-free survival and the frequency and severity of adverse events. The Phase II part was begun after determination of the recommended dosage from the Phase I part.

Assessment of the Response and Toxicity

Physical examination including cardiac symptoms, complete blood cell counts, serum chemistries and urinalysis was performed at the baseline and at least once every 2 weeks after the start of the treatment. Dynamic computed tomography or magnetic resonance imaging was undertaken to evaluate the response at 4- to 6-week intervals after the start of treatment. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (25). Toxicity was graded according to the National Cancer Institute common toxicity criteria, version 2.0. Progression-free survival was calculated from the first day of treatment to the appearance of evidence of tumor progression, clinical progression or last date of follow-up. The overall survival was calculated from the first day of treatment until death due to any cause or date of last follow-up. Survival data were analyzed using the Kaplan–Meier method.

Statistical Analysis

In the Phase II part, the primary endpoint was the response rate, and data from at least 19 patients were accrued. The threshold response rate was set at 5% and the expected response rate at 15%. If no responses were observed in the 19 patients and the upper limit of the 90% confidence interval (CI) did not exceed the expected rate of 15%, the UFM regimen was judged to have no activity against HCC. If response was confirmed in one or more of the 19 patients, the decision of whether or not to proceed to a further study using the UFM regimen was taken on the basis of other factors, such as the safety and rate of response, overall survival and time to progression in this study.

RESULTS

Patients

From April 2004 to April 2007, 25 patients were registered for the present study: 12 patients completed the Phase I part (Level 1: 3 patients, Level 2: 6 patients and Level 3: 3 patients). Nineteen patients who received the recommended dose (6 patients received this dose during the Phase I part) were analyzed during the Phase II part. Table 2 shows the baseline characteristics of the patients in the Phase I and Phase II parts of the study of the UFM regimen. There were 19 males and 6 females with a median age of 67 years. All the patients had a good ECOG PS score of 0–1. There were 21 (84%) and 4 (16%) patients with the Child–Pugh Stages A and B, respectively. Thirteen (68%) patients had extrahepatic metastasis, and the major sites of metastasis were lymph node [$n = 7$ (28%)] and lung [$n = 6$ (24%)].

Treatments

In the Phase I part, there was no occurrence of DLT at the Level 1 and Level 2 doses, but all of the three patients who received the Level 3 dose experienced DLT; two of these patients developed Grade 4 neutropenia and one patient developed Grade 3 creatinine elevation. The additional three patients at the Level 2 dose did not experience any DLT. Therefore, Level 3 was considered as the MTD and Level 2 (UFT 300 mg/m^2 and mitoxantrone 8 mg/m^2) as the recommended dose for the Phase II part.

At the recommended dosage level, a total of 69 courses of the UFM regimen were administered with a median of three courses to each patient (range, 1–8 courses). The dose intensity was 98.9% of the planned dosage for mitoxantrone and 97.9% for UFT.

The reasons for treatment discontinuation in the Phase I and Phase II parts were disease progression in 19 patients, liver dysfunction in 1 patient, DLT according to this protocol in 3 patients during the Phase I part and an over 6-week delay in the start of the next course because of the development of leukopenia in 2 patients. After abandoning the UFM

Table 2. Profile of hepatocellular carcinoma patients population

	Phase I	Phase II
No. of patients	12	19
Gender		
Male	9	14
Female	3	5
Age (years)		
Median	63	67
Range	56–78	56–77
Performance status		
0	11	7
1	1	12
Viral marker		
Hepatitis C antibody+	7	7
Hepatitis B antigen+	2	5
Previous treatment		
Surgical resection	4	10
Percutaneous ablation therapy	3	3
Transcatheter arterial chemoembolization	5	8
Transcatheter arterial infusion	3	5
Radiation therapy	1	2
None	3	3
Child–Pugh classification		
A	8	17
B	4	2
UICC tumor stage[a]		
III	4	6
IVa	3	1
IVb	5	12
Portal vein tumor thrombosis		
(+)	5	4
Extrahepatic metastasis		
Lymph node	5	7
Lung	0	6
Bone	0	3
Adrenal gland	0	1
Peritoneum	0	1
None	7	6

[a]The International Union Against Cancer, 6th edition.

regimen, 10 patients received the second-line treatment. Five patients received systemic chemotherapy, one patient received UFT alone and four patients received a combined chemotherapy with UFT and doxorubicin. Two patients received transcatheter arterial infusion with cisplatin, one patient received salvage TACE because of HCC rupture during the follow-up period, one patient received salvage radiofrequency ablation because of rapid growth of HCC that needed control and one patient received immnunotherapy.

Table 3. Toxicity

Toxicity grade	Phase I part									Phase II part		
	Level 1 ($n = 3$)			Level 2 ($n = 6$)			Level 3 ($n = 3$)			Level 2 ($n = 19$)		
	1–2	3	4	1–2	3	4	1–2	3	4	1–2	3	4
Hematological toxicity												
Leukopenia	2	1	0	0	2	0	0	1	1	4	9	3
Neutropenia	0	1	0	0	2	0	0	0	2	4	11	2
Thrombocytopenia	1	1	0	0	0	0	1	0	0	4	1	0
Anemia	0	0	0	1	0	0	0	0	0	1	0	0
Non-hematological toxicity												
Nausea	3	0	0	0	0	0	2	0	0	3	0	0
Anorexia	0	0	0	2	0	0	1	0	0	3	0	0
Elevated bilirubin	2	0	0	0	1	0	1	0	0	6	0	0
Hypoalbuminemia	1	0	0	0	0	0	0	0	0	1	0	0
Fatigue	0	0	0	0	0	0	1	0	0	1	0	0
Hyperpigmentation	0	0	0	0	0	0	0	0	0	1	0	0
Constipation	0	0	0	0	0	0	0	0	0	1	0	0
Elevated creatinine	0	0	0	0	0	0	0	1	0	0	0	0
Elevated AST	0	0	0	1	0	0	0	0	0	2	1	1[a]
Elevated ALT	0	0	0	1	0	0	0	0	0	1	2	1[a]
Liver dysfunction	0	0	0	0	0	0	0	0	0	0	0	1[a]

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]Death related to adverse event.

Toxicity

Table 3 summarizes the toxicities observed in the patients. At the recommended dose (level 2), the major Grade 3–4 hematological toxicities were leukopenia (63.2%) and neutropenia (68.4%). The most common non-hematological toxicities were elevated serum total bilirubin level (31.6%), elevated AST level (26.3%), elevated ALP level (26.3%) and anorexia (21.1%); however, no Grade 3–4 non-hematological toxicities were observed. One patient died of hepatic failure due to hepatitis B virus (HBV) reactivation.

Efficacy

Of the 19 patients who were administered the recommended dosage, 18 died during the follow-up period. All of the 19 patients administered the recommended dosage were evaluable for tumor response; of these, 1 patient achieved partial response (PR), with an overall response rate of 5.3% (95% CI, 0.0–26.0%). Eight patients (42.1%) had stable disease

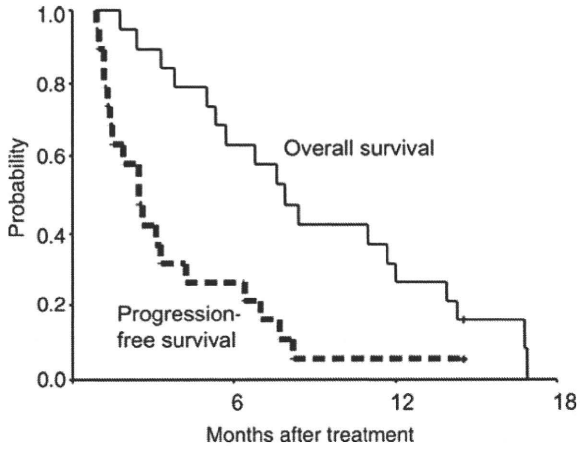

Figure 1. Overall survival and progression-free survival in 19 patients at the recommended dose. Tick marks indicate censored cases.

and 10 patients (52.6%) had progressive disease. The 1-year survival rate, median overall survival, median progression-free survival and time to progression were 26.3%, 8.4 months (95% CI, 5.4–11.4) and 2.5 months (95% CI, 1.5–3.5), respectively (Fig. 1).

DISCUSSION

Systemic chemotherapy for unresectable HCC is recognized as an important treatment modality, because some patients who have recurrent or very advanced disease are not suitable candidates for effective local treatments such as surgical resection, liver transplantation, local ablation therapy and TACE. Many patients with HCC have underlying chronic liver disease and impaired hepatic function, increasing the toxicity of standard doses of many chemotherapeutic agents and causing difficulty in delivering combination chemotherapies. The results, in terms of the therapeutic efficacy, of investigation of cytotoxic agents for advanced HCC have been disappointing, with few agents have yielded response rates of over 20%, and no cytotoxic agents have produced convincing survival benefits in the Phase III setting (26–28).

In Japan, only five anticancer agents, UFT, adriamycin, cytarabine, mitomycin and 5-FU, had been approved for the systemic chemotherapy of HCC by the Ministry of Health, Labor and Welfare of Japan before sorafenib has been approved. Among these drugs, the results of multiagent regimens containing both a fluoropyrimidine and an anthracycline antibiotic have shown favorable results for advanced HCC (22–24). Thus, it was expected that the combination of mitoxantrone and UFT (UFM regimen) would have effective anticancer activity, and we conducted a Phase I/II study to evaluate this regimen.

In the Phase I part, we determined the recommended dose of mitoxantrone as 8 mg/m^2 on day 1 and of UFT as 300 mg/m^2 from days 1 to 21 of a 28-day cycle. The DLTs observed at Level 3 were Grade 4 neutropenia (two patients) and Grade 3 creatinine elevation (one patient).

Patients with HCC tend to experience more severe myelosuppression and hepatic toxicity than those with other malignant diseases, because most have underlying cirrhosis, which is usually associated with compromised hepatic function, leukopenia and thrombocytopenia (24). In 19 patients treated at the recommended dose level, the most frequently encountered toxicities were leukopenia and neutropenia, which are well-known toxicities of the two drugs. When compared with that in trial of mitoxantrone or UFT for other malignancies, Grade 3 or 4 hematological toxicities occurred more frequently (29–31). However, these toxicities were reversible and generally well tolerated in patients with advanced HCC, except for one case of treatment-related death; this patient developed hepatic failure due to HBV reactivation, because no antiviral drug for HBV infection, such as lamivudine or entecavir, was given. This is a well-recognized complication in patients with HBV infection who received immunosuppressive therapy or chemotherapeutic agents (32,33). Thus, patients with HBV infection should receive prophylactic antiviral treatment before chemotherapy.

In the current study, 1 of the 19 patients showed a PR (response rate, 5.3%). However, the rate of progressive disease was 52.6%. In addition, the result of median time to progression was only 2.5 months. Those results were unfavorable when compared with those reported from other clinical trials (8,21–23). Therefore, this regimen is considered to be ineffective and cannot be recommended for use in clinical practice. There were several reasons for this negative result. One of the reasons was the number of anticancer drugs in the regimen. A regimen containing two drugs may have little activity, and three or more drugs may be needed to obtain activity against HCC, because many of the regimens that have been shown to exert anticancer effect against HCC contain three or more drugs. The other reason was the recommended doses of the drugs in this regimen. We set the criteria of DLT which had included Grade 4 neutropenia or leukopenia. Two patients experienced DLT based on these criteria. However, both recovered soon, with only observation. Therefore, the criteria may be too strict, although the two drugs have been used at these recommended doses for other malignancies. It may be possible to set higher dose levels to obtain higher antitumor effect.

Recently, increasing knowledge of the molecular pathogenesis of HCC as well as the introduction of molecular-targeted therapies has created an encouraging trend in the management of HCC. Combination regimens consisting of molecular-targeted agents such as sorafenib and cytotoxic agents have been reported as promising regimens for patients with advanced HCC and other malignancies (34–37). The UFM regimen itself has little antitumor activity, but the result may be useful in the setting of future clinical trials of cytotoxic agents used in combination with molecular-targeted agents.

In conclusion, the recommended dose was mitoxantrone at 8 mg/m^2 and UFT at 300 mg/m^2/day. A combined chemotherapy with mitoxantrone and UFT appeared to show

little activity in patients with advanced HCC, although this regimen was generally well tolerated. These findings do argue against the use of this regimen in clinical practice.

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Conflict of interest statement

None declared.

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今月のテーマ●胆管癌の進展度診断と治療戦略

胆管癌に対する化学療法

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要旨：胆管癌に対する化学療法は，通常，胆道癌の一部として胆嚢癌や乳頭部癌と同様の方法で行われ，わが国ではgemcitabineとS-1が広く用いられている．最近，gemcitabine単独治療とgemcitabine＋cisplatin併用療法（GC療法）によるランダム化比較試験が行われ，GC療法が胆道癌に対する標準治療と位置づけられている．さらにbevacizumabやcetuximabなどの分子標的薬を用いて上乗せ効果を狙った試みも行われている．一方，gemcitabine＋S-1併用療法でも良好な成績が報告されつつあり，ランダム化比較試験による検証が進められている．胆道癌の術後補助療法については現在まで標準的治療法は確立していない．わが国ではgemcitabineあるいはS-1を中心にいくつかの臨床試験が行われており，今後標準術後補助療法の確立が期待される．

索引用語：胆管癌，胆道癌，全身化学療法，分子標的薬，術後補助療法

はじめに

胆管癌は規約上，原発性肝癌に分類される肝内胆管癌と，胆道癌に分類される肝外胆管癌に分けられる[1)2)]．肝内胆管癌は原発性肝癌の4.1%を占めることから，がんの統計2009年によると年間罹患数は約1700人である[3)4)]．一方，肝外胆管癌は年間約11700人が新たに罹患している[4)]．予後については，切除例における5年生存率は肝内胆管癌28%～36%[5)～7)]，肝外胆管癌26%程度と部位によって差があるが，いずれも満足できるものではない[8)]．

胆管癌患者の予後の改善には有効な化学療法の確立と適切な適応が必須であり，胆道癌として臨床試験が行われてきた．現在，わが国ではgemcitabine（GEM）とtegafur/gimeracil/oteracil potassium配合剤（S-1）が広く用いられている．さらに，GEM＋cisplatinやGEM＋S-1の併用療法が試みられ，大規模な比較試験も行われてきている．本稿では胆管癌に対する化学療法の最近の動向について概説する．

I　胆道癌に対する化学療法の最近の動向

これまで，胆道癌に対する化学療法では，膵癌で用いられた薬剤が臨床試験として試みられることが多く，GEMが単剤あるいは併用療法として多くの臨床試験が行われてきた（Table 1）[9)～11)13)～17)19)20)]．わが国で行われたGEM単独の第II相試験では，奏効率17.5%，全生存期間（OS）中央値7.6カ月と[9)]，それまで胆道癌で主に用いられていたuracil/tegafur（UFT）やdoxorubicinなどに比べ良好な治療成績が得られ，2006年6月，胆道癌に対する保険適応が承認された．フッ化ピリミジン薬も多く用いられており，海外ではcapecitabine，わが国ではS-1が単独あるいはGEMとの併用で使われている（Table 1）．わが

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Systemic chemotherapy for cholangiocarcinoma

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Table 1. 切除不能胆道癌に対する最近の主な臨床試験

Regimen	n	Response rate	Median PFS	Median OS	Author (year)
Gemcitabine	40	17.5%	2.6mo	7.6mo	Okusaka (2006)[9]
S-1	19	21.0%	3.7mo	8.3mo	Ueno (2004)[10]
S-1	40	35.0%	3.7mo	9.4mo	Furuse (2008)[11]
Gemcitabine/capecitabine	45	31.1%	7mo	14mo	Knox (2005)[13]
Gemcitabine/capecitabine	45	31.8%	6mo	14mo	Cho (2005)[14]
Gemcitabine/S-1	35	34.3%	5.9mo	11.6mo	Sasaki (2010)[15]
Gemcitabine/oxaliplatin	33	35.5%	5.7mo	15.4mo	André (2004)[16]
Gemcitabine/oxaliplatin	31	26.0%	6.4mo	11mo	Harder (2006)[17]
Gemcitabine Gemcitabine/cisplatin	206 204	15.5% 26.1%	5.0mo* 8.0mo*	8.1mo** 11.7mo**	Valle (2010)[19]
Gemcitabine Gemcitabine/cisplatin	42 41	11.9% 19.5%	3.7mo 5.8mo	7.7mo 11.2mo	Furuse (2009)[20]

PFS：progression-free survival，OS：overall survival，*ハザード比 0.63（95%CI：0.51～0.77），$p < 0.001$，**ハザード比 0.64（95%CI：0.52～0.80），$P < 0.001$.

国で行われたS-1の前期および後期第II相試験では，奏効率 21～35%，OS中央値 8.3～9.4カ月と良好な治療成績が得られたことから[10][11]，2007年8月，胆道癌に保険適応が承認されている．2007年の胆道癌診療ガイドラインでは，切除不能胆道癌に対する化学療法は胆管炎などが十分コントロールされた全身状態の良好な患者を対象として，GEMあるいはS-1による化学療法が推奨されている[12]．

胆道癌における多剤併用療法では，主にGEMを基本薬剤としてフッ化ピリミジン剤，プラチナ系薬剤などの薬剤との併用療法が試みられている（Table 1）．特に英国で行われたGEM単独とGEM＋cisplatin併用（GC療法）のランダム化第II相試験ではGEM単独群の奏効率 15%，無増悪生存期間（PFS）中央値 4カ月に対し，GC療法群では奏効率 24%，PFS中央値 8カ月と併用療法の有用性が示唆され[18]，引き続いて大規模な第III相試験（ABC-02試験）が行われた．その結果，GEM単独群に比べ，GC療法群で有意な生存期間の延長が確認され（Figure 1），有害事象も両群で大きな差を認めなかった[19]．一方，わが国でもABC-02試験と同様のレジメンでランダム化比較試験（BT-22試験）が行われ，ほぼ同様の結果が2009年米国臨床腫瘍学会（ASCO）で報告された[20]（Table 1）．これらの試験ではGEMは通常の用法用量の 1000mg/m^2，30分点滴静注が用いられたが，cisplatinは1回 25mg/m^{2}と低用量で投与された．いずれの薬剤も週1回，2週連続投与後，1週休薬の3週を1サイクルとするレジメンである．Cisplatinの投与量を少なくしたことが毒性をマイルドにし，良い結果につながったと推察されている．今後，わが国でもこの用法用量によるGC療法が切除不能胆道癌に対する新しい標準治療となっていくものと考えられる．

以上のように，GC療法が進行胆道癌に対する標準治療と認められてきているが，同じプラチナ系薬剤であるoxaliplatinもGEMとの併用（Gemox療法）で同等以上の成績も報告されている（Table 1）[16][17]．インドにおいて緩和治療（BSC）と5-FU＋folnic acid（FUFA），Gemoxの3群による比較試験が行われ，OS中央値がBSC群 4.5カ月，FUFA群 4.6カ月，Gemox群 9.4カ月と，Gemoxにおいて有意な予後の改善が得られている（$p = 0.039$）[21]．

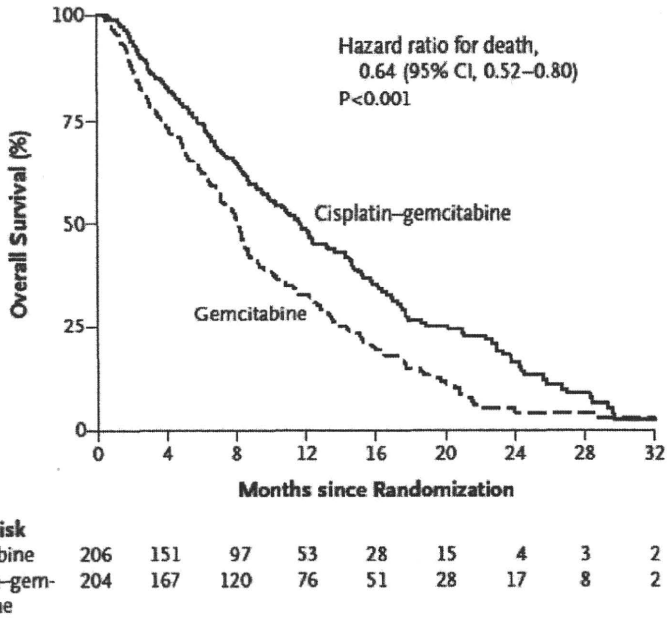

Figure 1. 切除不能胆道癌に対するgemcitabineとgemcitabine/cisplatinのランダム化比較試験（ABC-02試験）の生存曲線[19].

一方，GEMとフッ化ピリミジン薬，特にcapecitabineやS-1の併用でも有効性が報告されている（Table 1）．これらの第II相試験では11.6～14カ月のOS中央値が得られており[13)～15)]，GC療法とほぼ同等である．わが国では2010年4月現在，cisplatinは胆道癌に適応が承認されておらず，GEM＋S-1併用療法（GS療法）への期待も大きい．現在，日本臨床腫瘍研究グループ（JCOG）ではS-1単独治療とGS療法のランダム化比較第II相試験が行われ，すでに予定の100例の症例集積が終了している．

近年，がんの分子生物学，分子遺伝子学の進歩により，がん細胞に特徴的な遺伝子発現やがんの増殖・進展につながるシグナル伝達をターゲットとした新しい分子標的薬の開発が盛んに行われてきている．胆道癌においても，さまざまな分子標的の発現が確認され[22)]，VEGFRおよびEGFR阻害薬の有効性を示唆する基礎研究も出てきている[23)24)]．胆道癌における分子標的薬の開発は，単剤としてはerlotinibやsorafenibなどで第II相試験が行われているが，これまでのところ十分な成果は得られていない（Table 2）[25)～32)]．一方，EGFRに対する抗体薬cetuximabあるいはVEGFに対する抗体薬bevacizumabは，GEM＋oxaliplatin併用療法（Gemox）への上乗せ効果を狙った臨床試験が行われ，良好な治療成績が報告されている（Table 2）．Gemoxと Gemox＋cetuximabのランダム化比較試験も行われ，中間解析ではcetuximabの併用でPFSの延長が報告されている[32)]．

分子標的薬の効果予測因子として，erlotinibやgefitinibのEGFRチロシンキナーゼ阻害薬ではEGFR遺伝子の変異，cetuximabなど抗EGFR抗体薬ではK-ras遺伝子の変異が薬剤の有効性と大きな関係があることが示されている．胆道癌ではこれらを含めた細胞増殖に関するシグナル伝達路の発現や遺伝子変異などは，疾患による差を含め，十分検討されていない．これまで分子標的薬による大規模な臨床試験は行われておらず，今後，胆道癌での特徴を明らかにし，それに応じた分子標的薬の開発が期待される．

Table 2. 切除不能胆道癌に対する分子標的薬の治療成績

Regimen	n	Response rate	Median PFS	Median OS	Author (year)
Erlotinib	42	7%	2.6mo	7.5mo	Philip (2006)[25]
Lapatinib	17	0%	1.8mo	5.2mo	Ramanathan (2009)[26]
Sorafenib	36	6%	2mo	6mo	El-Khoueiry (2007)[27]
Sorafenib	46	2%	2.3mo	4.4mo	Bengala (2010)[28]
Bevacizumab/erlotinib	34	20%	–	–	Holen (2008)[29]
Gemcitabine/oxaliplatin/bevacizumab	35	40.0%	7.0mo	12.7mo	Zhu (2010)[30]
Gemcitabine/oxaliplatin/cetuximab	30	63.3%	8.3mo	12.7mo	Gruenberger (2009)[31]
Gemcitabine/oxaliplatin	51	16.7% (n = 18)	5.0mo	–	Malka (2009)[32]
Gemcitabine/oxaliplatin/cetuximab	50	11.1% (n = 18)	7.0mo	–	

PFS；progression-free survival, OS；overall survival.

Table 3. 胆管癌と胆嚢癌に対する化学療法の治療成績

Author (year)	Tumor site	n	Response rate	Tumor control rate	Median OS
Eckel (2007)[33]	Cholangiocarcinoma	500	20.2%[a]	59.7%	9.3mo[b]
	Gall bladder cancer	471	34.4%	60.5%	7.2mo
Yonemoto (2007)[34]	Intrahepatic cholangiocarcinoma	126	6.0%	54.0%	8.4mo[c]
	Extrahepatic cholangiocarcinoma	97	5.7%	54.2%	10.2mo[d]
	Gall bladder cancer	169	10.6%	57.4%	6.5mo

OS；overall survival, [a] p = 0.904, [b] p = 0.048, [c] p = 0.072, [d] p = 0.029.

II 化学療法における胆管癌の特徴

胆道癌に対する化学療法では，通常，肝内および肝外胆管癌，胆嚢癌，乳頭部癌が一括して臨床試験で扱われている．しかし，これらの疾患は，薬物に対する感受性や予後など異なる点も多く，別のがん種として検討する必要性もしばしば指摘される．1985年から2006年までに公表された104の第II相試験（112治療群，2810例）を解析したpooled analysisでは，胆嚢癌で有意に高い奏効率が得られるものの，予後は胆管癌で良好であることが示されている（Table 3）[33]．またわが国で行われた全身化学療法施行例の後ろ向き検討でも胆嚢癌で奏効率が高いものの，胆管癌で化学療法後の予後が良い傾向を認めている（Table 3）[34]．

前向き研究でも胆管癌と胆嚢癌を比較した成績がいくつか報告されている．最近のGEM単独とGC療法の比較試験（ABC-02試験）のサブグループ解析によるハザード比は，胆管癌ではGEM群とGC療法群で差は認めなかったのに対し（0.73，95%CI：0.43～1.23），胆嚢癌ではGC療法で良好な成績が得られている（0.61，95%CI：0.42～0.89）[19]．つまり，胆管癌と胆嚢癌では薬剤による効果の発現が異なる傾向を認めている．一方，わが国で行われたUFT＋doxorubicin併用療法の第II相試験において，85例での予後因子を解析したところ，performance status，に続いて，胆嚢癌が非胆嚢癌に比べ強い予後不良因子として挙げられた（Table 4）[35]．

以上のように，胆管癌では化学療法による直接

Table 4. UFT＋DXR 併用化学療法施行切除不能胆道癌例における予後因子[35]

Variables		n	Median OS	Hazard ratio	95%CI	*p*-value
ECOG PS	0	61	8.2mo	1		0.001
	1	24	4.3mo	2.52	1.44 ～ 4.42	
Disease site	ICC/ECC/AV	43	8.4mo	1		0.014
	GBC	42	5.4mo	1.88	1.14 ～ 3.12	
T-factor	T1-3	62	8.1mo	1		0.035
	T4	23	5.0mo	1.93	1.05 ～ 3.56	
LDH	＜300	67	8.1mo	1		0.043
	≧300	18	4.8mo	1.85	1.02 ～ 3.35	
CA19-9	＜1000	59	8.1mo	1		0.067
	≧1000	26	5.2mo	1.73	0.96 ～ 3.11	

OS：overall survival，PS：performance status，ICC：intrahepatic cholangiocarcinoma，ECC：extrahepatic cholangiocarcinoma，GBC：gallbladder cancer，AV：ampulla of Vater cancer.

の抗腫瘍効果は低いものの生存期間は比較的長いことが示唆されている．胆道癌の化学療法を行う際には，疾患の差を念頭に置いた実施や臨床試験の計画が必要である．

III 術後補助療法の展望

胆管癌をはじめとする胆道癌では根治切除が行われた症例でも早期再発が多く，その予後は不良である．したがって治癒率の向上のためには再発防止を目的とした有効な術後補助療法の確立が必要である．胆道癌ではこれまで術後補助療法のランダム化比較試験はほとんど行われておらず，わが国で行われた術後補助化学療法（mytomycin C＋5-FU 併用）と手術単独の比較試験のみである[36]．この試験では，膵癌 158 例，胆管癌 118 例，胆嚢癌 112 例，乳頭部癌 48 例の適格例について疾患ごとに解析され，胆嚢癌では 5 年生存率は化学療法群 26.0% に対し，切除単独群 14.4% と化学療法群で有意に予後良好であった，と報告されている．一方，胆管癌では 5 年生存率は化学療法群 26.7% に対し，切除単独群 24.1% と差を認めていない．切除不能胆道癌における化学療法の成績を考えると，術後補助療法では直接の抗腫瘍効果の出やすい胆嚢癌の方が，有用性が期待できることが示唆されている．

切除不能胆道癌で使われている GEM と S-1 が術後補助療法でも有用性が期待され，わが国では現在 GEM 単独あるいは GEM 併用療法による臨床試験がいくつか行われている．その中で，NPO 法人名古屋外科支援機構による第 III 相試験（BCAT）は胆管癌のみを対象とした GEM と手術単独のランダム化比較試験であり，300 例の症例集積を予定して実施中である．一方，英国では capecitabine と observation による第 III 相試験が 360 例を目標に行われている．今後，切除不能胆道癌と同様，エビデンスに基づいた治療法が確立されるものと考えられる．一方では，これらの大規模な第 III 相試験はいずれも 300 例以上の症例を必要としており，比較的患者数の少ない胆道癌では完遂が容易ではない．また胆道癌の手術では胆道再建や消化管バイパスなどがほぼ全例で行われることから，胆管炎や消化管障害などのリスクもあり，他の疾患とは違った慎重な開発が必要と考えられる．

おわりに

胆道癌に対する治療上，化学療法の役割は大きく，予後の改善には有効な化学療法の確立が必須である．最近の数年，GEM や S-1 の導入により，胆道癌の予後は明らかに改善しつつあり，GC 療

法のように大規模な比較試験に基づいた標準治療も確立してきた．一方，胆道癌の中で，胆管癌と胆嚢癌は化学療法の治療成績は異なることも示唆されている．さらに，胆管癌や胆嚢癌の区別だけでなく，分子生物学的な遺伝子変異も念頭においた薬剤の開発も必要と考えられる．

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Transcatheter arterial infusion chemotherapy with cisplatin–lipiodol suspension in patients with hepatocellular carcinoma

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Abstract
Purpose The aim of this study was to investigate the antitumor efficacy of treatment, identify prognostic factors, and construct a prognostic index in patients with hepatocellular carcinoma treated by transcatheter arterial infusion chemotherapy (TAI) using cisplatin suspended in lipiodol.
Methods We analyzed the outcomes in a total of 94 consecutive patients with previously untreated hepatocellular carcinoma who were treated by TAI using cisplatin suspended in lipiodol.
Results Twenty-seven patients (29%) showed complete response and 21 patients (22%) showed partial response, with an overall response rate of 51% (95% confidence interval, 41–61%). The median survival time was 2.5 years and the proportions of survivors at 1, 2, and 5 years were 81.6, 65.2, and 18.3%, respectively. The results of multivariate analysis indicated a significant association of serum albumin $\geq$3.0 g/dL, maximum tumor size $\leq$3.0 cm, absence of ascites, and unilateral distribution of the tumors with a favorable survival. For clinical application, we also propose a prognostic index based on a combination of these prognostic factors. Based on this index, the patients were classified into three groups: those with good, intermediate, and poor prognosis. The median survival times in these three groups were 4.3, 2.7, and 1.1 years, respectively ($p < 0.01$).
Conclusions TAI with cisplatin suspended in lipiodol exhibited favorable tumor efficacy and survival in patients with hepatocellular carcinoma. The prognostic factors identified and the index proposed based on these factors may be useful for predicting life expectancy, determining treatment strategies, and designing future clinical trials.

Keywords Hepatocellular carcinoma · Transcatheter arterial infusion chemotherapy · Cisplatin · Prognosis

Abbreviations

HCC	Hepatocellular carcinoma
TAE	Transcatheter arterial chemoembolization
TAI	Transcatheter arterial infusion chemotherapy
CT	Computed tomography
AFP	Serum alpha-fetoprotein
PIVKA II	Protein induced by vitamin K absence or antagonist-II
CR	Complete response
PR	Partial response

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, and its incidence is continuing to increase worldwide. However, the prognosis of advanced HCC remains unsatisfactory [1]. Curative therapies such as resection, liver transplantation, and local ablative treatments may offer a chance of improved life

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expectancy, but these treatment modalities are applicable to only a small proportion of all HCC patients. Transcatheter arterial chemoembolization (TAE) has been recognized as an effective palliative treatment option for patients with advanced HCC, because two meta-analyses [2, 3] of seven randomized controlled trials [4–10] showed that TAE significantly improves the survival of unresectable HCC patients with preserved hepatic function [1]. Transcatheter arterial infusion chemotherapy (TAI) is also often used for the treatment of advanced HCC, but a consensus regarding the most effective chemotherapeutic regimen has not yet been reached [11, 12]. Lipiodol, a lipid lymphographic agent, is selectively retained by HCC tissues for prolonged periods in comparison with non-cancerous tissues, and is therefore commonly mixed with anticancer agents to allow these agents to be retained for prolonged periods of time in the target tumor [13–15]. In a randomized controlled trial of TAE and TAI with zinostatin stimalamer and lipiodol, TAE did not yield superior survival as compared to TAI in patients with advanced unresectable HCC [16]. Our previous analysis also revealed that TAE did not significantly improve the survival of patients with HCC in comparison with TAI using cisplatin suspended in lipiodol, even though TAE is known to have higher antitumor efficacy than TAI [17]. Thus, TAI may have a higher efficacy on survival compared to TAE. If the appropriate indications for TAI can be expanded, additional embolization may not be necessary in some patients, considering that TAE has more deleterious effects on the liver functions than TAI [17, 18]. However, proper patient selection for TAI with lipiodol has not yet been fully investigated, although those for TAI without lipiodol [19–21] and for TAE [22–24] have been frequently analyzed. Analysis of prognostic factors would suggest appropriate patient selection for TAI. The present study was conducted to investigate the antitumor efficacy of the treatment, and to evaluate a number of variables that may affect survival in patients with HCC treated by TAI using cisplatin suspended in lipiodol; we have proposed a prognostic index in patients treated with TAI based on the results of our analyses.

Materials and methods

Patients

Between October 1987 and May 1996, 94 consecutive patients with previously untreated HCC were treated by transcatheter arterial infusion chemotherapy using cisplatin suspended in lipiodol at Kumamoto University Hospital, Japan. The study subjects were patients who were judged to be suitable candidates for TAI (Table 1). HCC was diagnosed on the basis of histological examination or distinctive findings on computed tomography (CT) and/or angiography, associated with elevated serum levels of serum alpha-fetoprotein (AFP) or protein induced by vitamin K absence or antagonist-II (PIVKA II). Pretreatment evaluation included a complete medical history and careful physical examination. The laboratory procedures included complete

Table 1 Patient characteristics

	No of patients (%)
Host-related variables	
Age (years)	
Median [range]	64 [41–81]
Gender	
Male	62 (66%)
Blood transfusion	
Present	28 (30%)
Alcohol abuse[a]	
Present	11 (12%)
Smoking habit[b]	
Present	31 (33%)
Hepatitis B surface antigen	
Positive	14 (15%)
Hepatitis C antibody	
Positive	76 (81%)
Ascites	
Present	14 (15%)
Child-Pugh class	
A	45 (48%)
B	48 (51%)
C	1 (1%)
Tumor-related variables	
Number of tumors	
Multiple	53 (56%)
Tumor distribution	
Unilateral	70 (74%)
Maximum tumor size (cm)	
Median [range]	2.9 [1.5–12.0]
Portal vein invasion	
Present	7 (7%)
Alpha-fetoprotein (ng/mL)	
Median [range]	36.9 [1.9–17,100]
PIVKA II (mAU/mL)	
Median [range]	30 [0–6,000]
Other variables	
Modified Japan Integrated Stage	
Median [range]	2 [0–5]

PIVKA II protein induced by vitamin K absence or antagonist-II

[a] Ethanol intake ≥80 g/day for ≥5 years

[b] >20 cigarettes/day for >10 years

differential blood count, biochemistry tests, viral markers, including serum hepatitis B surface antigen and serum hepatitis C antibody, and tumor markers, including the serum levels of AFP and PIVKA II. Before treatment, a chest X-ray and ultrasonography and CT of the abdomen were obtained to evaluate the extent and size of the tumors and to exclude the presence of extrahepatic metastasis. The number, size, and distribution of the tumors were examined by CT and/or angiography. Written informed consent was obtained from all the patients prior to the start of the treatment.

Treatment procedure

Following conventional visceral angiography, TAI was performed by selectively introducing a catheter into the proper, right or left hepatic artery, or a branch of the artery feeding the tumor and injecting cisplatin suspended in lipiodol (iodized oil; Guerbet, Paris, France). The dose of the drug was determined based on the tumor size and liver function. The cisplatin suspension in lipiodol was prepared by the following procedure [25]: cisplatin powder, produced by evaporating water and sodium chloride from cisplatin solution, was sterilized by heating and subsequently suspended in lipiodol with a mortar and pestle under sterile conditions. The content of cisplatin in the lipiodol was adjusted to 20 mg/mL.

After the treatment, follow-up examinations, including CT, tumor marker measurement, and serum biochemistry, were performed, first at one month after the treatment completion and subsequently every 3–4 months. The transcatheter arterial treatments were repeated when relapse of the treated lesions and/or new hepatic lesions were seen.

Evaluation of the antitumor efficacy

The antitumor effect was assessed by contrast-enhanced CT or magnetic resonance imaging at one month after the treatment. Lipiodol accumulation in the tumor was regarded as representing necrotic tissue, because earlier studies have shown that areas on the CT showing lipiodol retention correspond to necrotic areas in the tumors [13–15]. We defined complete response (CR) as disappearance or 100% necrosis of all tumors, and partial response (PR) as >50% reduction and/or necrosis in the sum of all measurable tumors. Progressive disease was defined as more than 25% enlargement in the sum of all lesions and/or the appearance of any new lesions. Stable disease was considered as any disease that did not qualify for classification as CR, PR or progressive disease.

Factors analyzed

The relationships of pretreatment clinical variables to survival were investigated by univariate and multivariate analyses. The pretreatment variables were chosen based on their possible effects on the prognosis and tumor response indicated by previous investigations [1–12, 16–30] or suggested by our own clinical experience. Each of the variables, which were classified as host-related or tumor-related, was divided into two subgroups in accordance with clinically meaningful values for easy application in clinical practice, as shown in Table 2.

Overall survival was measured from the date of initial treatment to the date of death or last follow-up. Survival curves were calculated by the Kaplan–Meier method, and differences in survival were evaluated by the log rank test. The Cox proportional hazard model was used to determine the most significant variables related to survival. Forward and backward stepwise regression procedures based on the partial likelihood ratio were used to determine the major independent predictors of survival. A prognostic index based on the regression coefficients derived from all variables identified by the multivariate analysis was constructed. Stratification of the patients was conducted on the basis of this prognostic index. All p values presented in this report are of the two-tailed type. Differences at $p < 0.05$ were considered to be significant.

Results

Patient characteristics

The characteristics of all the 94 patients are shown in Table 1. There were 62 males (66%) and 32 females (34%), with a median age of 64 (range 41–81) years. There were 45 patients (48%), 48 patients (51%) and 1 patient (1%) with Child-Pugh stage A, B, and C [29], respectively. Fifty-three patients (56%) had multiple tumors, and the median maximum tumor size was 2.9 (range 1.5–12.0) cm. The median modified Japan Integrated Stage [30] was 2 (range 0–5). The median number of courses of TAI was two (range 1–9) during the follow-up period, and the median follow-up duration was 2.5 years (range 0.2–8.4 years). The median dose of cisplatin at first TAI was 50 (range 20–150) mg per treatment.

Treatment efficacy and survival

Twenty-seven patients (29%) showed CR and 21 patients (22%) showed PR, with an overall response rate of 51% (95% confidence interval, 41–61%). The median survival time was 2.5 years, and the proportions of survivors at 1, 2, 3, and 5 years were 81.6, 65.2, 39.8, and 18.3%, respectively (Fig. 1). The cause of death was tumor progression in 47 patients, hepatic failure in 25 patients, rupture of esophageal varices in 4 patients, and other causes in 6