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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 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

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.

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 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

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.

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 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

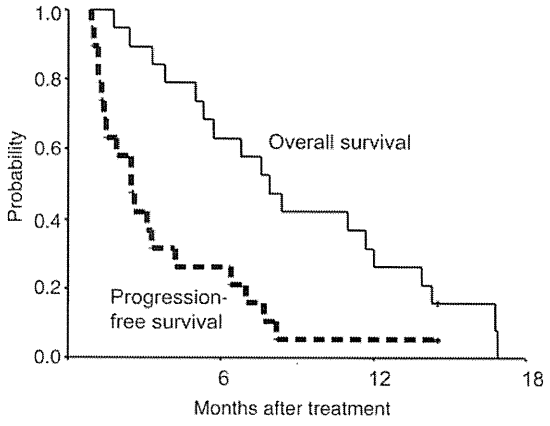

Figure 1. Overall survival and progression-free survival in 19 patients at the recommended dose. Tick marks indicate censored cases.

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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ORIGINAL ARTICLE

Phase I/II study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy (FGS) in gemcitabine-refractory pancreatic cancer patients

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Abstract
Purpose There is no standard regimen for gemcitabine (Gem)-refractory pancreatic cancer (PC) patients. In a previous phase II trial, S-1 was found to exhibit marginal efficacy. Gem administration by fixed dose rate infusion of 10 mg/m^2/min (FDR-Gem) should maximize the rate of intracellular accumulation of gemcitabine triphosphate and might improve clinical efficacy. We conducted the phase I/II of FDR-Gem and S-1 (FGS) in patients with Gem-refractory PC.
Methods The patients received FDR-Gem on day 1 and S-1 orally twice daily on days 1–7. Cycles were repeated every 14 days. Patients were scheduled to receive Gem (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels in the phase I: 800/80 (level 1), 1,000/80 (level 2), 1,200/80 (level 3) and 1,200/100 (level 4). Forty patients were enrolled in the phase II study at recommended dose.
Results The recommended dose was the level 3. In the phase II, a partial response has been confirmed in seven patients (18%). The median overall survival time and median progression-free survival time are 7.0 and 2.8 months, respectively. The common adverse reactions were anorexia, leukocytopenia and neutropenia.
Conclusion This combination regimen of FGS is active and well tolerated in patients with Gem-refractory PC.

Keywords Chemotherapy · Pancreatic carcinoma · Second-line · Gemcitabine · S-1 · Salvage · Fixed dose rate infusion

Introduction

Gemcitabine monotherapy or gemcitabine-containing combination chemotherapy is the standard first-line therapy for advanced pancreatic cancer. In the recent phase III study, the first-line FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group [4]. However, the FOLFIRINOX regimen was quite toxic (e.g., 5.4% of patients had grade 3 or 4 febrile neutropenia), and a survival benefit was shown only among a highly select population with a good performance status, an age of 75 years or younger, and normal or nearly normal bilirubin levels [13]. Therefore, this combination therapy was considered to be one of the treatment options for patients in good general condition, and gemcitabine remains the mainstay of care for patients with advanced pancreatic cancer. However, after disease progression during first-line gemcitabine-containing chemotherapy, the

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options for further anticancer treatment are limited. S-1 is an orally administered anticancer drug that consists of a combination of tegafur, 5-chloro-2,4-dihydroxypyridine and oteracil potassium in a 1 : 0.4 : 1 molar ratio [27]. The antitumor effect of S-1 has already been demonstrated in a variety of solid tumors including pancreatic cancer [7, 11, 12, 14, 20, 21, 25, 26, 32, 33]. In patients with chemo-naïve pancreatic cancer, an overall response rate of 21.1% was achieved, and the median time-to-progression and median overall survival period were 3.7 and 8.3 months, respectively [32]. In gemcitabine-refractory metastatic pancreatic cancer, our recent phase II study of S-1 yielded results that demonstrated marginal activity including a response rate of 15%, a median progression-free survival time of 2.0 months and a median overall survival time of 4.5 months, with a favorable toxicity profile [17]. In addition, other reports also demonstrated marginal antitumor activity [1, 28]. Gemcitabine administration via infusion at a fixed dose rate of 10 mg/m^2/min (FDR-Gem) has been found to increase the intracellular drug concentrations, compared with gemcitabine at a standard dose rate infusion over a period of 30 min. A recent phase II study of combination therapy consisting of FDR-Gem and oxaliplatin (GEMOX) yielded results that demonstrated activity in gemcitabine-refractory advanced pancreatic cancer [5], although oxaliplatin is inactive against pancreatic cancer when used as a single agent [6]. The increased intracellular concentrations of gemcitabine as a result of FDR infusion and/or the synergistic effect of gemcitabine and oxaliplatin may play an important role in the antitumor effect of GEMOX. This finding is of interest when considering the effect of combination therapy consisting of FDR-Gem and some other agent that exhibits a synergistic effect with gemcitabine in patients with metastatic pancreatic cancer who failed standard dose rate gemcitabine.

The inhibition of ribonucleotide reductase by gemcitabine is considered to enhance the effect of the 5-FU metabolite 5-FdUMP by reducing the concentration of its physiological competitor [10]. Preclinical studies have demonstrated a synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells [3, 23]. S-1 is a fluoropyrimidine, and several phase II studies of S-1 and gemcitabine combination therapy have yielded results that demonstrated a promising activity in chemo-naïve advanced pancreatic cancer patients, including a response rate of 32–48% and a median survival times of 7.89–12.5 months [16, 18, 19, 31].

Therefore, we conducted the present phase I/II study to determine the recommended doses of FDR-Gem and S-1 (FGS) to use for combination therapy and to evaluate the toxicity and efficacy at the recommended doses in patients with gemcitabine-refractory pancreatic cancer.

Materials and methods

Eligibility criteria

The eligibility criteria were histologically proven pancreatic adenocarcinoma with measurable metastatic lesions, disease progression during gemcitabine-based first-line chemotherapy, age 20 years or over, ECOG performance status of 0–2 points, more than 2-week interval between the final dose of the prior chemotherapy regimen and study entry, adequate bone marrow function (leukocyte count $\geq$ 3,500/mm^3, neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, hemoglobin concentration $\geq$ 9.0 g/dL), adequate renal function (serum creatinine level $\leq$ 1.1 mg/dL) and adequate liver function (serum total bilirubin level $\leq$ 2.0 mg/dL, transaminase levels $\leq$ 100 U/L). Patients with obstructive jaundice or liver metastasis were considered eligible if their total bilirubin level $\leq$ 3.0 mg/dL and transaminase levels could be reduced to 150 U/L by biliary drainage. The exclusion criteria were regular use of phenytoin, warfarin or flucytosine, history of fluorinated pyrimidine use, severe mental disorder, active infection, ileus, watery diarrhea, interstitial pneumonitis or pulmonary fibrosis, refractory diabetes mellitus, heart failure, renal failure, active gastric or duodenal ulcer, massive pleural or abdominal effusion, brain metastasis, and active concomitant malignancy. Pregnant or lactating women were also excluded. Written informed consent was obtained from all patients. This study was approved by the institutional review board of the National Cancer Center of Japan.

Treatment

Considering the patients' quality of life, we adopted biweekly schedule. Gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) was administered by FDR intravenous infusion of 10 mg/m^2/min on day 1. S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was administered orally twice daily on day 1 to day 7, followed by a 1-week rest. Treatment cycles were repeated every 2 weeks until disease progression or unacceptable toxicity occurred. If blood examination revealed leukocytopenia $<$ 2,000/mm^3, thrombocytopenia $<$ 75,000/mm^3, total bilirubin $>$ 3.0 mg/dL, aspartate aminotransferase or alanine aminotransferase level $>$ 150 U/L, or creatinine $>$ 1.5 mg/dL, both gemcitabine and S-1 were withheld until recovery. If a patient experienced dose-limiting toxicity (DLT), the dose of gemcitabine and S-1 was reduced by one level in the subsequent cycle. If a rest period of more than 15 days was required because of toxicity, the patient was withdrawn from the study. Patients were scheduled to receive gemcitabine and S-1 at four dosage levels (Table 1). Two dosage levels of S-1 were established according to the body

Table 1 Dosage levels of gemcitabine and S-1

Dosage level	Gemcitabine	S-1
Level 0	600 mg/m^2/60 min	Dosage A
Level 1[a]	800 mg/m^2/80 min	Dosage A
Level 2	1,000 mg/m^2/100 min	Dosage A
Level 3	1,200 mg/m^2/120 min	Dosage A
Level 4	1,200 mg/m^2/120 min	Dosage B

[a] Starting dosage

surface area as dosage A, about 80 mg/m^2/day, and dosage B, about 100 mg/m^2/day (Table 2). At the first dose level (level 1), gemcitabine was administered at a dosage of 800 mg/m^2 administered as a 80-min infusion, and S-1 was administered at dosage A. At the next dose level (level 2), the gemcitabine dosage was increased to 1,000 mg/m^2 administered as a 100-min infusion, and S-1 was administered at the same dosage. At the next dose level (level 3), the gemcitabine dosage was increased to 1,200 mg/m^2 administered as a 120-min infusion, and S-1 was administered at the same dosage. At the final dosage level (level 4), gemcitabine administered at the same dosage, and S-1 was administered at dosage B.

Study design

This study was an open-label, four-center, single-arm phase I/II study performed in two steps. The objective of step 1 (phase I) was to evaluate the frequency of DLT during first 2 cycles (4 weeks) and then use the frequency of DLT to determine which of the four dosages tested to recommend (Table 1). At least 3 patients were enrolled at each dosage level. If DLT was observed in the initial three patients, up to three additional patients were entered at the same dosage level. The highest dosage level that did not cause DLT in 3 of the 3 or $\geq$3 of the 6 patients treated at that level during the first two cycles of treatment was considered the maximum-tolerated dosage (MTD). DLT was defined as (1) grade 4 leucopenia or grade 4 neutropenia or febrile neutropenia, (2) grade 4 thrombocytopenia or thrombocytopenia requiring transfusion, (3) grade 3 or 4 non-hematological toxicity excluding hyperglycemia and electrolyte disturbances, (4) serum transaminases levels, γ-glutamyl transpeptidase level and alkaline phosphatase level $\geq$10 times UNL, (5) serum creatinine level $\geq$ 2.0 mg/dL and (6) any toxicity that necessitated a treatment delay of more than 15 days. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In step 2, the recommended dosages (RD) of FGS were then administered, and the effect of this combination therapy on objective tumor response was evaluated in patients who were given the RD (phase II). The number of patients to be enrolled in phase II was determined by using a SWOG's standard design (attained design) [8, 9]. The phase II included the patients who received the RD in the step 1. The null hypothesis was that the overall response rate would be $\leq$5%, and the alternative hypothesis was that the overall response rate would be $\geq$20%. The α error was 5% (one-tailed), and the β error was 10% (one-tailed). The alternative hypothesis was established based on the preferable data in previous reports [5, 15, 24, 30, 34]. Interim analysis was planned when 20 patients were enrolled. If none of the first 20 patients had a partial response or complete response, the study was to be ended. If a response was detected in any of the first 20 patients, an additional 20 patients were to be included in a second stage of accrual to more precisely estimate the actual response rate. If the number of objective responses after completing the trial was 5 or more among the 40 patients, then we would reject the null hypothesis and conclude that FGS was effective, and we would proceed to the next large-scale study. The severity of adverse events and progression-free survival and overall survival were investigated as secondary objectives in phase II.

Table 2 Dosage of S-1 (tegafur equivalent)

Body surface area (m^2)	Dosage A ($\fallingdotseq$80 mg/m^2/day)	Dosage B ($\fallingdotseq$100 mg/m^2/day)
<1.25	40 mg × 2/day	50 mg × 2/day
1.25–<1.5	50 mg × 2/day	60 mg × 2/day
$\geq$1.5	60 mg × 2/day	75 mg × 2/day

Results

Patient characteristics

Between June 2006 and March 2009, 49 patients were enrolled in this study. Fifteen patients (level 1: 3 patients, level 2: 3 patients, level 3: 6 patients, level 4: 3 patients) were enrolled into the phase I (STEP 1), and an additional 34 patients were enrolled into the phase II (STEP2) at dose level 3. Table 3 shows the baseline characteristics of the patients in step 1 and step 2. A total of the 40 patients who were given the recommended dose, 6 patients and 34 patients who entered into the study at phase I and phase II, respectively, were evaluated for efficacy and detailed safety profile.

Phase I (STEP 1)

No DLT occurred during the first 2 cycles (4 weeks) at level 1 or level 2. At dose level 3, three patients were

Table 3 Patient characteristics

Characteristic	Step 1				Step 2	Total at the recommended dose (level 3)
	Level 1	Level 2	Level 3	Level 4	Level 3	
No. of patients	3	3	6	3	34	40
Age, years						
Median	66	58	64	62	63.5	64
Range	55–69	51–58	48–71	52–70	40–80	40–80
Sex, *n* (%)						
Male	1 (33)	3 (100)	4 (67)	1 (33)	19 (56)	23 (58)
Female	2 (67)	0	2 (33)	2 (67)	15 (44)	17 (48)
ECOG performance status, *n* (%)						
0	2 (67)	2 (67)	5 (83)	2 (67)	22 (65)	27 (68)
1	1 (33)	1 (33)	1 (17)	1 (33)	12 (35)	13 (33)
Primary tumor, *n* (%)						
Head	1 (33)	2 (67)	2 (33)	2 (67)	17 (50)	19 (48)
Body/tail	2 (67)	1 (33)	4 (67)	1 (33)	17 (50)	21 (53)
Metastatic site, *n* (%)						
Liver	3 (100)	3 (100)	6 (100)	1 (33)	25 (74)	31 (78)
Lung	1 (33)	0	0	2 (67)	7 (21)	7 (18)
Peritoneum	1 (33)	1 (33)	0	1 (33)	11 (32)	11 (28)
Lymph node	0	2 (67)	0	0	11 (32)	11 (28)
Tumor stage at the start of prior treatment, *n* (%)						
Locally advanced	0	0	0	1 (33)	7 (21)	7 (18)
Metastatic	3 (100)	3 (100)	6 (100)	2 (67)	27 (79)	33 (83)
Prior treatment, *n* (%)						
Gemcitabine alone	3 (100)	3 (100)	5 (83)	3 (100)	26 (76)	31 (78)
Gem + Axitinib	0	0	0	0	2 (6)	2 (5)
Gem + Erlotinib	0	0	1 (17)	0	6 (18)	7 (18)

evaluated first, and none developed DLT. Since all 3 patients experienced DLT at dose level 4 (grade 4 neutropenia in two patients, grade 3 stomatitis in one patient), 3 additional patients were evaluated at dose level 3. A DLT (grade 4 neutropenia) was experienced by 2 of the 3 patients in this additional cohort in dose level 3, and dose level 3 was determined to be the MTD. Based on these results, the RD was determined to be level 3.

Phase II (efficacy and safety profile in the 40 patients treated at dose level 3)

In step 2, the RD of FDR-Gem and S-1 was administered to an additional 34 patients, and a total 40 patients were treated at dose level 3 to evaluate the objective tumor response to this combination therapy. As of the date of the analysis, the protocol treatment had been concluded in 39 of the 40 patients, and a total of 286 courses (median: 5 courses; range 1–31 courses) had been administered at level 3. The actual mean weekly dose administered were gemcitabine 545 mg/m^2/week (90.8% of planned dosage) and 90.1% of planned dosage of S-1. Dose reduction was required in 10 patients because of grade 4 neutropenia (five patients), grade 3 fatigue (1 patient), grade 2 fatigue with grade 2 appetite loss (one patient), grade 2 nausea (two patients) and grade 3 rash (1). The reasons for treatment discontinuation in phase II were radiological disease progression (33 patients), clinical disease progression (two patients), recurrent grade 4 neutropenia despite dose reduction due to grade 4 neutropenia (two patients), grade 4 myocardial infarction (one patients) and patient request to return to his distant hometown (one patient). All patients who discontinued treatment because of adverse events recovered from the toxicities after discontinuation. Twelve patients received third-line chemotherapy after discontinuation of FGS: S-1 monotherapy in four patients, gemcitabine + S-1 combination therapy on another treatment schedule in three patients, chemoradiotherapy with S-1 in one patient and new molecularly targeted agents in four patients who participated in a different clinical trial. Twenty-two patients received best supportive care, the other five patients transferred to another hospital, and no

information is available about their treatment after discontinuation of FGS.

Toxicity

All patients in steps 1 and 2 were evaluated for toxicity. In step 1, grade 3/4 non-hematological toxicity was observed in two patients (grade 3 fatigue during the third course in one patient, grade 3 stomatitis during the second course in one patient). No grade 4 leukocytopenia was observed at any dose level, but grade 4 neutropenia was observed in one out of three patients at dose level 1, none of the three patients at dose level 2, two of the six patients at dose level 3 and all three of the patients at dose level 4. Grade 3 thrombocytopenia was observed in one patient at dose level 2.

Table 4 summarizes the toxicities in the 40 patients who received the RD (level 3). All 40 eligible patients were assessable for toxicities, and FGS combination therapy at the RD was generally well tolerated. The most common toxicities were leukocytopenia (60%) and neutropenia (60%), but most of these toxicities were tolerable and reversible. Grade 4 neutropenia was noted as hematological toxicity in five patients (13%). Grade 3 non-hematological toxicities consisted of fatigue (one patient), vomiting (one patient), rash (one patient) and liver abscess (one patient). The patient who developed the grade 3 liver abscesses recovered after appropriate treatment with intravenous antibiotic alone. One female patient, who had hypercholesterolemia and history of smoking of 30 cigarettes/day, experienced a grade 4 acute myocardial infarction on day 1 of the third course of treatment, after gemcitabine had been administered but before the start of oral S-1. Emergency coronary angiography showed total occlusion of the left anterior descending coronary artery. The patient recovered from the cardiogenic shock due to myocardial infarction after coronary stent implantation and appropriate supportive treatment. S-1 monotherapy for the pancreatic cancer was started about 1 month after the infarction. No other severe or unexpected toxicities were noted in any of the patients.

Table 4 Treatment-related adverse events among the 40 patients who received the recommended dosages: highest grade reported during the treatment period

	Grade				Grade 1–4	Grade 3–4
	n					
	1	2	3	4	*n* (%)	*n* (%)
Hematological toxicities						
Leukocytes	11	4	9	0	24 (60)	9 (23)
Neutrophils	10	1	8	5	24 (60)	13 (33)
Hemoglobin	5	11	1	0	17 (43)	1 (3)
Platelets	11	2	1	0	14 (35)	1 (3)
Non-hematological toxicities					(0)	
Aspartate aminotransferase	8	1	0	0	9 (23)	0 (0)
Alanine aminotransferase	8	3	0	0	11 (28)	0 (0)
Alkaline phosphatase	5	2	0	0	7 (18)	0 (0)
Total bilirubin	3	0	0	0	3 (8)	0 (0)
Fatigue	15	2	1	0	18 (45)	1 (3)
Nausea	13	4	0	0	17 (43)	0 (0)
Vomiting	8	1	1	0	10 (25)	1 (3)
Anorexia	19	6	0	0	27 (68)	0 (0)
Stomatitis	4	0	0	0	4 (10)	0 (0)
Alopecia	8	0	–	–	8 (20)	–
Diarrhea	7	2	0	0	9 (23)	0 (0)
Rash	3	4	1	0	8 (20)	1 (3)
Hyperpigmentation	9	1	–	–	10 (25)	–
Hand-foot skin reaction	1	2	0	0	3 (8)	0 (0)
Watery eye	2	0	0	–	2 (5)	0 (0)
Hoarseness	1	0	0	0	1 (3)	0 (0)
Infection liver abscess	0	0	1	0	1 (3)	1 (3)
Myocardial infarction	0	0	0	1	1 (3)	1 (3)

Three patients died within 30 days after the final dose of the study drug. All 3 of the deaths were attributed to disease progression, and there were no treatment-related deaths.

Efficacy

It was possible to assess all 40 eligible patients who received the RD for response. Thirty-four patients had died by the completion of the follow-up period. There were no complete responses, but a partial response was achieved in seven patients (18, 95% confidence interval, 7.3–32.8%). Stable disease was noted in 19 patients (48%) and progressive disease in 14 patients (35%). Tumor responses to second-line FGS therapy are classified according to the tumor responses to first-line gemcitabine in Table 5. Three of 10 patients whose best response was progression disease in first-line chemotherapy achieved partial response in FGS therapy. The median progression-free survival time was 2.8 months. The median overall survival time after the start of second-line therapy was 7.0 months (range 1.3–18.9+), and the 1-year survival rate was 18% (Fig. 1). The median overall survival time after the start of first-line therapy was 13.9 months (range 5.2–31.4).

Table 5 Objective tumor response

Response (2nd line)	*n* (%)	Response (1st line)		
		PR	SD	PD
PR	7 (18)	1	3	3
SD	19 (48)	3	12	4
PD	14 (35)	2	9	3
Total	40 (100)	6	24	10

Response rate: 18% (95% CI: 7.3–32.8)

RECIST criteria

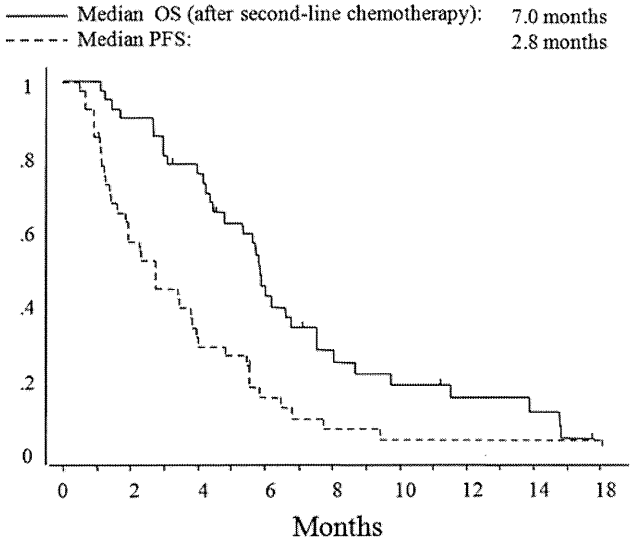

Fig. 1 Survival curves. Survival ($n = 40$). Progression-free survival (*dashed line*) and overall survival time (*solid line*) curves of patients with gemcitabine-refractory pancreatic cancer receiving systemic chemotherapy with FGS

Discussion

In the last decade, several clinical trials (mainly phase II) have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine or a gemcitabine-based combination regimen. The results of a randomized trial ($n = 168$) comparing fluorouracil and folinic acid versus oxaliplatin, fluorouracil and folinic acid (OFF) indicated that OFF improved progression-free survival and overall survival as a second-line chemotherapy. The median progression-free survival time and median survival time of OFF were 3 and 6 months, respectively [22]. In the present study, FGS yielded a median progression-free survival time of 2.8 months and a median overall survival time of 7.0 months, similar to the data mentioned above. Furthermore, the response rate of 18% in the present study was above the pre-established boundary (objective response in five or more of the 40 patients) required for the regimen to be considered effective. However, the gap between the median overall survival time and the median progression-free survival time in the present study was relatively large. Although the reason for this gap is unknown, a bias arising from the selection of patients with a good general condition or with a small tumor burden may explain these findings.

Whether gemcitabine as an FDR infusion is active even after progression during treatment with the standard 30-min administration of gemcitabine was the critical clinical question examined in this study. Differentiating between the relative roles of gemcitabine and S-1 in overcoming tumor resistance is difficult. The efficacy and survival data obtained in the present study seem to be better than those of previous studies for oral fluoropyrimidine monotherapy as a salvage chemotherapy for advanced pancreatic carcinoma (Table 6) [1, 2, 17, 28, 29]. However, since all the data were obtained in single-arm studies, a randomized study is needed to make these suggestions reliable. Furthermore, whether the combined regimen in the present study is superior to other regimens, such as the OFF regimen, remains an essential clinical question.

Safety and convenience as well as antitumor efficacy are critically important issues with regard to second-line chemotherapy. One patient experienced an acute myocardial infarction. Although she had other risk factors, such as a smoking habit and hyperlipidemia, a relation between gemcitabine and the acute myocardial infarction cannot be ruled out because gemcitabine had been administered on the day of the infarction. The toxicity profile of FGS

Table 6 Comparison between the current study and previous studies of oral fluoropyrimidine monotherapy as salvage chemotherapy for advanced pancreatic carcinoma

Study	References	Phase	Regimen	*n*	PR + CR (%)	Median PFS (months)	Median OS (months)
Morizane et al.	[12]	II	S-1	40	15	2.0	4.5
Abbruzzese et al.	[29]	II	S-1	45	0	1.4	3.1
Sudo et al.	[31]	II	S-1	21	9.5	4.1	6.3
Todaka et al.	[32]	Retrospective	S-1	52	4	2.1	5.8
Boeck et al.	[30]	II	Capecitabine	39	0	2.3	7.6
Morizane et al.	Current study	II	FGS	40	18	2.8	7.0

therapy in the other patients was acceptable, and the most common grade 1–4 adverse reactions were anorexia (68%), leukocytopenia (60%) and neutropenia (60%), although most episodes were tolerable and reversible. The safety profile in this study suggests that FGS can be safely administered to pancreatic cancer patients even in a second-line setting, at least in select populations. The biweekly schedule allows enough time to recover from myelosuppression and non-hematological toxicities before the following cycle, enabling patients to receive treatment as scheduled. Actually, the relative dose intensities of gemcitabine and S-1 in our study were high (90.8 and 90.1%, respectively). Furthermore, because of the biweekly schedule, patients do not need to come to the hospital for treatment as often compared with the first-line standard schedule of gemcitabine therapy. Our new treatment schedule may therefore improve the patients' quality of life during anticancer treatment.

We concluded that combination therapy consisting of gemcitabine as a fixed dose rate infusion and S-1 (FGS) provided a promising antitumor activity and tolerable toxicity in patients with gemcitabine-refractory metastatic pancreatic cancer. A larger randomized controlled trial is needed to confirm the clinical benefits of FGS following gemcitabine failure.

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分子標的治療

肝細胞がんに対する分子標的治療の現況

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要　旨

進行肝細胞がんに対して，マルチキナーゼ阻害薬ソラフェニブにより初めて生存期間の延長が得られたことから，現在，ソラフェニブが肝機能良好かつ肝外転移，血管浸潤および血管塞栓術不応例に対する標準治療となっている．頻度の高い有害事象は手足皮膚反応，皮疹，下痢，高血圧，肝障害などであり，早期に発現することが多く，適切な対応が求められる．血管塞栓術との併用や肝切除などの補助療法としても臨床試験が行われている．

はじめに

原発性肝がんのほとんどを占める肝細胞がんでは，肝切除など局所治療が中心であり，薬物療法の役割は極めて限定的である．しかし，進行がんで発見された症例では肝外転移を認める例も少なくなく，また局所療法を繰り返す間に肝外転移を認める例も増えてきている．このような局所治療の効果が期待できない例に対しては，これまで有効な治療法は確立していなかった．

最近の新規薬剤の開発は，がんの進展，増殖にかかわるさまざまな分子生物学的特徴に基づいた分子標的薬が主流となっており，肝細胞がんにおいても，マルチキナーゼ阻害薬ソラフェニブの大規模なランダム化比較試験によって生存期間の延長が初めて確認され[1]，我が国でも 2009 年 5 月，保険適応が承認されている．

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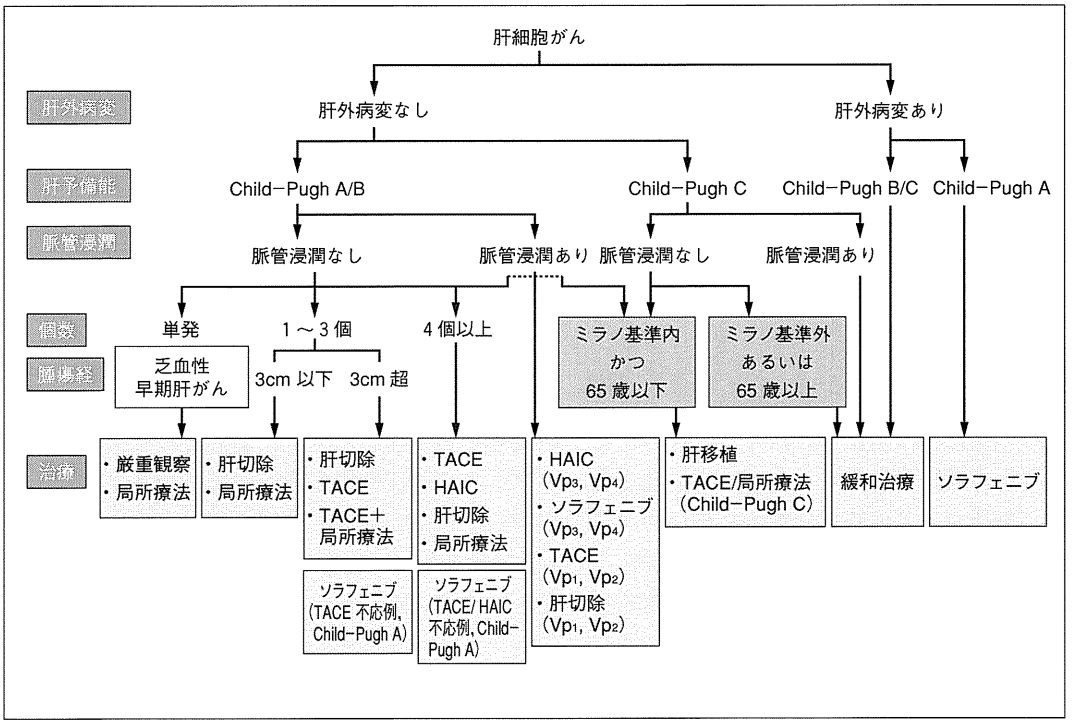
肝細胞がんに対する治療選択

肝細胞がんの治療選択は，がんの進行度と肝障害度に応じて決定される（図1）．肝細胞がんでは肝外転移が少ないこと，肝内病変のコントロールが肝機能維持や延命に繋がることなどから，肝切除，ラジオ波焼灼療法（RFA），肝動脈化学塞栓療法（TACE）の局所治療が優先される．薬物療法については肝動注療法が，TACE の適応とならない進行がんに選択されてきた．全身化学療法としては，ソラフェニブが初めて生存期間の延長を示したことから，肝機能が良好，かつ肝外転移例，および血管塞栓術不応例に対する標準治療と位置づけられている[2]．

図1 肝細胞がんの治療アルゴリズム（文献[2]より改変引用）



略語：巻末の「今月の略語」参照

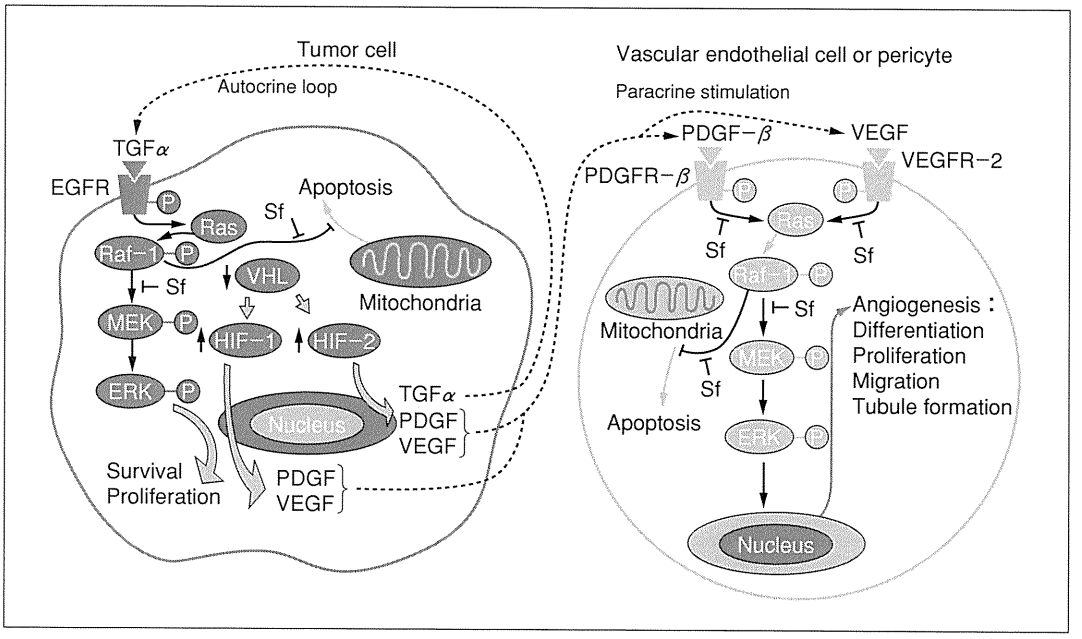
ソラフェニブの臨床試験

ソラフェニブは，EGF受容体の下流であるRafキナーゼとVEGFR-1～3，PDGFR-βなど血管新生のシグナル伝達を標的とするマルチキナーゼ阻害薬である（図2）[3]．さまざまな固形がんを対象として行われた第Ⅰ相臨床試験において，肝細胞がんの患者1例で奏効例が認められたため[4]，肝細胞がん患者を対象に第Ⅱ相臨床試験が実施された[5]．対象はChild-Pugh AとBの肝細胞がん患者で，3段階に症例集積が行われ，137例が登録された．その結果，奏効率は2.2%と低かったものの，増悪までの期間（TTP）中央値5.5ヵ月，全生存期間（OS）中央値9.2ヵ月と有効性が示唆された．安全性についても，グレード3の毒性は疲労感9.5%，下痢8.0%，手足皮膚反応5.1%と忍容性が得られた[5]．

我が国では，日本人肝細胞がん患者での薬物動態，安全性，推奨用量などを明らかにする目的で，第Ⅰ相臨床試験が行われた[6]．その結果，他の固形がん患者や米国・ヨーロッパの患者と同様の薬物動態および忍容性が確認され，推奨用量も400mg，1日2回と決定された．症例数は少ないものの，有効性も同等であった．

進行肝細胞がんを対象としたソラフェニブによるランダム化比較試験として，これまでヨーロッパ中心のSorafenib HCC Assessment Randomized Protocol（SHARP）試験とアジア中心のAsia-Pacific試験の2つが行われている[1][7]．いずれの試験でも，OS，TTPともにソラフェニブで良好な治療成績が得られ，有意差を認めている（表1）．

図2　ソラフェニブの作用機序（文献[3]より改変引用）



略語：巻末の「今月の略語」参照

表1　進行肝細胞がん患者におけるソラフェニブによるプラセボ対照無作為化第Ⅲ相試験（SHARP 試験および Asia-Pacific 試験）の治療成績

	SHARP study[2]		Asia-Pacific study[7]	
	Sorafenib	Placebo	Sorafenib	Placebo
N	299	303	150	76
Median overall survival	10.7mo[*1]	7.9mo	6.5mo[*3]	4.2mo
Time to progression	5.5mo[*2]	2.8mo	2.8mo[*4]	1.4mo
Overall response				
Partial response	2.3%	0.7%	3.3%	1.30%
Stable disease	71%	67%	54%	27.6%
Progressive disease	18%	24%	30.7%	54%
Overall incidence of treatment-related adverse events	80%	52%	81.9%	38.7%

Hazard ratio（sorafenib/placebo）：[*1]0.69（p＜0.001），[*2]0.58（p＜0.001），[*3]0.68（p＝0.014），[*4]0.57（p＝0.0005）

有害事象とその対策

これまでの臨床試験で報告された頻度の高い有害事象は，手足皮膚反応，下痢，疲労，高血圧，食思不振などである（表2）．我が国の第Ⅰ相臨床試験では，主な非血液毒性として皮疹，手足皮膚反応，下痢，疲労感，リパーゼ・アミラーゼの膵酵素上昇などが1/3以上の症例で認められている．経口剤による治療は原則として外来通院で開始されることが多く，頻度の高い有害事象についてはあらかじめ患者に十分な説明を行い，対策を講じ

表2 ソラフェニブの臨床試験で認められた主な有害事象

有害事象	SHARP 試験 (n=299)	Asia−Pacific 試験 (n=150)	日本の第Ⅰ相試験 (n=27)
皮疹	16%	20%	56%
下痢	39%	26%	56%
手足皮膚反応	21%	45%	44%
疲労	22%	20%	37%
体重減少	9%	—	30%
掻痒	8%	—	30%
脱毛	14%	25%	29%
食欲低下	14%	13%	22%
高血圧	5%	19%	19%
皮膚乾燥	8%	—	11%
悪心	11%	11%	—
嘔吐	5%	—	—
声の変化	6%	—	—
肝機能異常	＜1%	—	—
腹痛	8%	—	—
出血	7%	—	—

ておく必要がある．皮疹，手足皮膚反応，高血圧などは治療開始から1～2週の早期に起こることが多く，初めの4週間は少なくとも週1回のチェックが必要である．

臨床試験ではそれほど問題にならなかった肝障害が，製造販売後の全例調査で多数認められている．特に，肝細胞がん患者において肝性脳症，肝不全が治療開始後早期に発現し，注意勧告が行われた．200 IU/m*l* を超えるAST/ALT の上昇，あるいは 2.0mg/d*l* 以上の総ビリルビン値の上昇を認めた場合は直ちに中止するなど，適切な対応が必要である．

日常生活に支障の出るような手足皮膚反応，重篤な肝障害，持続する高度の下痢，その他重篤な非血液毒性が認められた場合は，直ちに休薬する．回復後，治療を継続するメリット・デメリットを考慮し，可能なら減量して治療を再開することができる．減量方法は，

ソラフェニブ 400mg/回，1日2回内服
→400mg/回，1日1回内服

ソラフェニブ 400mg/回，1日1回内服
→400mg/回，1日1回隔日内服

が推奨されている．

適応拡大に向けた臨床試験

肝細胞がんではほとんどの症例で局所療法が行われることから，局所療法の成績の向上を目的に，分子標的薬の併用が試みられている．ソラフェニブは，TACE あるいは切除や RFA など局所壊死療法との併用療法が実施されている．

TACE 後のソラフェニブのプラセボ対照比較試験は，日本と韓国の共同試験として実施された．この試験では，TACE 実施後 CT で 25% 以上の壊死効果あるいは腫瘍縮小が得られた症例を対象として，ソラフェニブとプラセボに割り付けられた．TACE の効果判定は中央判定としたため，TACE からランダム化までの期間が中央値で9週間以上を要するなど課題が残った．主要評価項目は増

悪までの期間であったが，有意な差は認められず，ソラフェニブによる TACE 後の病勢進行を抑える効果は確認できなかった[8]．ソラフェニブの SHARP 試験の結果が出る前に開始された試験であり，まだ薬剤に慣れておらず，有害事象中止が多かったこと，TACE からソラフェニブ治療までの間が長くなってしまったこと，などが原因に挙げられた．

TACE 後早期に血清 VEGF が増加することから，VEGF の抑制が治療成績の向上に繋がることも示唆されており[9]，TACE 後早期から VEGFR 阻害薬の投与が望ましいとされている．現在，他の分子標的薬ブリバニブや TUS-68 などで TACE との併用による国際治験が実施されており，いずれも TACE 後早々に投与が行われるような試験デザインになっている．

肝細胞がんでは早期の場合，肝切除あるいは RFA などが適応となり，根治が可能である．しかし，いったん根治が得られても高率に再発を認め，再発防止の補助療法が求められてきた．これまで，術後補助療法薬としてインターフェロンをはじめ，ビタミン K_2，レチノイドなどが試みられてきたが，標準治療は確立していない．現在，ソラフェニブを用いた切除あるいは局所壊死療法後のプラセボ対照ランダム化比較試験（国際共同試験）が実施され，すでに症例集積は終了している．

おわりに

肝細胞がんにおいて，ソラフェニブにより初めて生存期間の延長に寄与する薬物療法が確立した．一般臨床で広く用いられているが，副作用などで長期間の使用が難しいなど課題も多い．現在，新たな分子標的薬の開発や適応拡大に向けた取り組みが進められており，肝がん治療の選択肢がさらに増えるものと期待される．

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Molecular Targeted Therapy for Hepatocellular Carcinoma

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