trolled clinical trial.

Design

Two groups, a low-dose and high-dose bFGF group, have been set (**Figure 1**). In the initial step (Step 1), three patients will be enrolled in the low-dose group. After confirming the safety in the low-dose group, patients will be randomized to the low-dose or high-dose bFGF group in Step 2. Randomization-based comparison between dose groups can achieve significant improvements in accuracy and lack of bias. This comparison can provide useful information for designing and conducting future trials.

Setting and participants

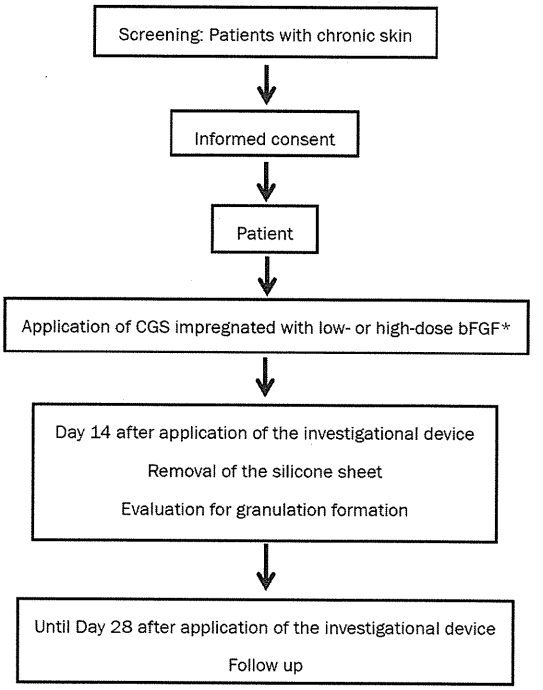
This study is being conducted at Kyoto University Hospital. Patients with chronic skin ulcers are referred by physicians and also identified through a number of wound care clinics in Kyoto Prefecture and surrounding prefectures.

Inclusion criteria

1). Patients aged 20 years or older at informed consent. 2). Presence of chronic skin ulcers as below: not healing for at least 4 weeks with conventional treatments; skin graft is not expected to take; can be completely covered by a 70 mm × 100 mm device. 3). If chronic skin ulcers are present on lower extremities, the skin perfusion pressure must be ³ 30 mmHg at a site proximal or distal to those ulcers. 4). Written informed consent.

Exclusion criteria

1). Have any of the following systemic diseases: uncontrolled diabetes mellitus (defined by HbA1c ³ 10%) according to latest laboratory data obtained within 28 days before registration); requiring continued use of oral corticosteroid therapy (> 20 mg/day prednisolone equivalent); a history of malignant tumor with disease-free interval of 5 years or less. 2). Have a history of allergy to porcine-derived products, collagen, gelatin, bFGF, anesthetic drugs, disinfectants, etc. 3). Have participated in another clinical trial/study within the past three months. 4). Have participated in this study previously. 5). Women meeting any of the following: do not agree to avoid pregnancy during the study; currently pregnant or possibly pregnant; currently breastfeeding. 6). Other patients judged by the investigator or sub-investigator to be inappropriate as a subject of this study.



*: Step 1 (non-randomized): low-dose bFGF (n=3); Step 2 (randomized): low-dose bFGF (n=7) and high-dose bFGF (n=7)

Randomization

In Step 2, patients will be randomized to either the low-dose or high-dose bFGF group at a ratio of 1:1 without stratification. Randomization will be performed using a computer-generated random sequence to ensure equal allocation to the two dose groups by a statistician of the independent data center (Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital).

Interventions

Preparations of CGS impregnated with bFGF

CGS is the modification of conventional bilayered artificial dermis (Pelnac; Gunze Co., Ltd, Kyoto, Japan) and consists of an upper silicone sheet (0.1mm in thickness) and lower sponge (3 mm in thickness) [20]. In this study, the lar-

ger CGS (82 mm × 120 mm) will be used. Two different dose bFGF concentrations of 7 μg/cm^2 (low dose) or 14 μg/cm^2 (high dose) will be used. On the day of study therapy, the investigator or sub-investigator will prepare CGS impregnated with bFGF in the operating room

Application of CGS impregnated with bFGF

This therapy will be started within 28 days of enrollment. After debridement of the chronic skin ulcers, CGS impregnated with bFGF of 7 μg/cm^2 or 14 μg/cm^2 and cut according to the shape of the wound will be applied and sutured to surrounding skin.

Dressing changes and silicone sheet removal

After the application of CGS, dressings will be changed as necessary. Patients will be hospitalized until Day 7 to ensure stabilization of the applied CGS and may be discharged on Day 8 after application according to the condition of the wound. On Day 14 after application, the sutures and silicone sheet of CGS will be removed. After silicone film removal, subsequent therapy may be started.

Subsequent therapy

The use of bFGF or another collagen-based artificial skin will be prohibited until Day 28 after application. The use of ointments, wound dressings and skin grafting will be allowed. After completion of the study period (Day 29 after investigational device application and onward), no particular restrictions will be imposed.

Digital photograph for healing assessment

Using a digital camera, digital images of the wounds will be taken with a calibrator (CASMATCH; BEAR Medic Corp., Tokyo, Japan) placed on the skin adjacent to the wound. The color and size of image will be adjusted using the CASMATCH and image editing software (Adobe Photoshop; Adobe Systems) to assess the wound and granulation areas. As with the primary endpoint, the granulation tissue evaluation committee members will assess the wound and granulation areas.

Primary endpoint

The primary endpoint is "wound bed improvement."

Granulation tissue is wound connective tissue, which forms at the beginning of wound healing [26]. This highly fibrous tissue is usually pink because numerous small capillaries invade granulation tissue to supply oxygen and nutrients. The appearance of granulation tissue is a good sign of healing because when a wound starts granulating, it means that the healing process of the wound is starting [26-28]. The area of granulation tissue will be measured as the granulation formation area in this study. An unhealed area is defined as an area with no epithelialization and no granulation formation. In this study, the percentage of wound bed improvement is defined as the value (%) calculated from the sum of the granulated and epithelialized areas on Day 14 divided by the baseline wound area after debridement on Day 0 multiplied by 100, and the patient is diagnosed with wound bed improvement if the wound bed improvement indicator is 50% or higher. The use of 50% or more as the cutoff for the wound bed improvement indicator is based on the pressure ulcer healing assessment scale by the Japanese Society of Pressure Ulcers [28, 30, 31].

Secondary endpoints

1). Adverse events and adverse reactions. 2). Percentage of "wound bed improvement". 3). Percentage of wound reduction: The percentage of wound area reduction is defined as the value (%) calculated from the wound area of the ulcer on Day 14 divided by the baseline wound area after debridement on Day 0 multiplied by 100. 4). Percentage of granulation area: The percentage of granulation area is defined as the value (%) calculated from the granulation area divided by the wound area on Day 14 multiplied by 100.

Blinding

The baseline wound area, the wound area on Day 14 and the granulation area on Day 14 will be independently measured under blinding by central review. Patients will be unblinded, and unblinded investigators will apply CGSs and change dressings.

Sample size

This study will be conducted to determine whether CGS impregnated with bFGF is promising for the treatment of chronic skin ulcers, as evaluated based on wound bed improvement as

Table 1. Schedule of study assessments and evaluations

		Treatment			Observation
Clinical assessments, testing and investigations	Day of enrollment	Day of application/ reapplication	← →	Day of silicone sheet removal (Day 14)	Day 28 after application/ reapplication
Clinical history	○				
Physical examination	○				
Eligibility criteria check	○				
Informed consent	○				
Blood test	○			○	○
Skin perfusion pressure	○				
Investigational device application		○			
Clinical assessment of the wound	○	○		○	○
Digital photograph of wound	○	○		○	○
Wound evaluation				●	
Data submission of treatment and AE etc.		○		○	○
Observation of AE		○	← ○ →	○	○

○: required; ●: Wound area measurements, granulation area measurements (wound for efficacy evaluation and wounds for study therapy)

the primary endpoint. Primary analyses will be conducted using all data treated with CGS in Step 1 and Step 2. Since debridement and conventional therapies rarely lead to wound bed improvement in this patient population, the null hypothesis tested in this study is that the proportion of patients with wound bed improvement is 10% or less. The null hypothesis is also supported by previous trials [32-34]. In consideration of the minimum clinically important difference, the expected proportion of patients with wound bed improvement in this study is set to 50% or more. When exact testing based on binomial distribution is conducted with a one-sided significance level of 2.5% and a statistical power of 90% or higher, the required number of subjects is 14. Allowing for a drop-out rate of 20% or less, the total number of patients for registration is 17, specifically 3 patients in Step 1 and 14 patients in Step 2.

Study schedule

The schedule of study assessments and evaluations is shown in **Table 1**. The study period will be from the day of informed consent to 28 days after investigational device application. The study period will be from the day of investigational device application to 28 days after investigational device application. Data to evaluate the efficacy and safety of this study will be collected at enrollment, baseline, and Day 14 of the treatment phase and Day 28 of the observation phase.

Statistical analysis

Patients who have been registered for the study and who have undergone investigational device application at least once will be included in the full analysis set (FAS) and the safety analysis

set. From the FAS, however, patients will be excluded if they have serious protocol violations or International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP) violations (failure to obtain consent, major study procedure violations) or if they are found to be ineligible after registration.

Wound bed improvement

Wound bed improvement is the primary endpoint of this study. The primary analysis will be conducted for the FAS using exact test based on binomial distribution with a null proportion of 10% and a one-sided significance level of 2.5%. The 95% confidence interval of the proportion of patients with wound bed improvement will be calculated using an exact method based on binomial distribution.

Percentage of wound bed improvement, would reduction and granulation area

Using the FAS, the descriptive statistics will be calculated. The interval estimation will be conducted under the assumption that this endpoint follows normal distribution.

Adverse events related to the application of the device

Using the safety analysis set, the frequency/incidence of adverse events and adverse events that can be causally related to the investigational device in the safety analysis set will be calculated by event and severity.

Ethical considerations

This study is being conducted in compliance with the ICH-GCP and in agreement with the latest revision of the Declaration of Helsinki, Pharmaceutical Affairs Law and all applicable Japanese laws and regulations, as well as any local laws and regulations and all applicable guidelines. This protocol and any amendments have Institutional Review Board approval at Kyoto University Hospital.

Subject consent

Informed consent will be obtained from all potential study participants using the IRB-approved informed consent form. The clinical investigator informs the potential study subject of all pertinent aspects of the study. The subject must sufficiently understand the contents of the information form before providing written consent. The consent form must be dated and signed by both the investigator and the participant. Subjects are also informed that their medical care will not be affected if they do not choose to participate in this study. The consent form will be retained at Kyoto University Hospital and the information form and a copy of the consent form will be handed to the participant. Whenever the investigator obtains information that may affect the participant's willingness to continue participation in the study, the investigator or sub-investigator will immediately inform the participant and record this, and reconfirm the participant's willingness to continue participation in the study.

Adverse events

This study is being conducted according to the ICH-GCP. Adverse events and serious adverse events information will be documented according to the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0.

Results and discussion

This study has been designed to address the safety and efficacy of novel treatment for chronic skin ulcers using a modified artificial dermis, CGS, that can sustain bFGF. This study will be the first randomized controlled trial to evaluate the efficacy of CGS and the appropriate concentration of bFGF impregnation for treatment of increasing non-healing ulcers. Some bioengineered skin substitutes that provide growth factors secreted by living cells have been reported to be effective for chronic skin ulcers, although they are costly and access is limited to only a few areas and countries. Both CGS and bFGF are freeze-dried and can be kept well and stored at room temperature. These are off-the-shelf products and the procedure of impregnation is simple; therefore, we can use this combination therapy anywhere when needed. If successful, this intervention may lead to substantial and important changes in the management of chronic skin ulcers, such as diabetes ulcers and venous leg ulcers

Acknowledgements

This work was supported by a grant from the

Japan Science and Technology Agency.

Address correspondence to: Dr. Naoki Morimoto, Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Kyoto University, 54, Kawahara-cho Shogoin, Sakyo-ku, Kyoto 606-8507, Japan Tel: +81-75-751-3613; Fax: + 81-75-751-4340; E-mail: mnaoki22@kuhp.kyoto-u.ac.jp

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(8)953–958
doi:10.1093/jjco/hyr090
Advance Access Publication 29 June 2011

Multicenter Phase II Study of Gemcitabine and S-1 Combination Therapy (GS Therapy) in Patients With Metastatic Pancreatic Cancer†

Hideki Ueno[1,*], Takuji Okusaka[1], Junji Furuse[2,3], Kenji Yamao[4], Akihiro Funakoshi[5], Narikazu Boku[6], Shinichi Ohkawa[7], Osamu Yokosuka[8], Katsuaki Tanaka[9], Fuminori Moriyasu[10], Shoji Nakamori[11] and Tosiya Sato[12]

[1]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, [2]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital East, Chiba, [3]Department of Internal Medicine, Medical Oncology, Kyorin University School of Medicine, Tokyo, [4]Department of Gastroenterology, Aichi Cancer Center Hospital, Aichi, [5]Department of Gastroenterology, National Kyushu Cancer Center, Fukuoka, [6]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, [7]Division of Hepatobiliary and Pancreatic Medical Oncology, Kanagawa Cancer Center Hospital, Kanagawa, [8]Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, Chiba, [9]Gastroenterological Center, Yokohama City University Medical Center, Kanagawa, [10]Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, [11]Department of Surgery, National Hospital Organization, Osaka National Hospital, Osaka and [12]Department of Biostatistics, Kyoto University School of Public Health, Kyoto, Japan

*For reprints and all correspondence: Hideki Ueno, Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: hiueno@ncc.go.jp

Received May 9, 2011; accepted June 2, 2011

Objective: The aim of this multicenter Phase II study was to assess the efficacy and toxicity of gemcitabine and S-1 combination therapy for metastatic pancreatic cancer.
Methods: Chemotherapy-naïve patients with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. Gemcitabine was administered at a dose of 1000 mg/m^2 over 30 min on days 1 and 8, and oral S-1 at a dose of 40 mg/m^2 twice daily from days 1 to 14, repeated every 3 weeks.
Results: A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44.4% (95% confidence interval: 30.9–58.6%). The median progression-free survival was 5.9 months (95% confidence interval: 4.1–6.9 months) and the median overall survival was 10.1 months (95% confidence interval: 8.5–10.8 months) with a 1-year survival rate of 33.0%. The major Grade 3–4 toxicities were neutropenia (80%), leucopenia (59%), thrombocytopenia (22%), anorexia (17%) and rash (7%). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia ≥Grade 3.
Conclusions: Gemcitabine and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer. A randomized Phase III study to confirm the efficacy of gemcitabine and S-1 combination therapy is ongoing.

Key words: pancreatic cancer – Phase II – chemotherapy – gemcitabine – S-1

†Part of the content of this report was presented at the ASCO 2007 meeting in the poster presentation (abstract 4550).

INTRODUCTION

Pancreatic cancer is a highly malignant disease and the fifth most common cause of cancer death in Japan. Approximately 80% of patients are ineligible for surgery at diagnosis and more than half of patients have metastatic disease.

Gemcitabine has been the standard chemotherapeutic agent for metastatic pancreatic cancer on the basis of a Phase III study showing clinical and survival benefits over 5-fluorouracil (5-FU) (1). However, the efficacy of gemcitabine monotherapy for advanced pancreatic cancer is limited; most clinical trials have shown response rates of around 10% with a median overall survival of 6–7 months (2–5). Therefore, numerous studies have attempted to increase the efficacy of chemotherapy, but almost all the regimens evaluated in Phase III studies have failed to show survival benefits over gemcitabine. To date, only two randomized trials, gemcitabine plus erlotinib and combination therapy of 5-FU/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) have shown significant prolongation of overall survival (6,7). However, the reported difference in median survival between the gemcitabine plus erlotinib group and the gemcitabine-only group was small (6.24 versus 5.91 months). The results of the FOLFIRINOX trial are more impressive than those of gemcitabine plus erlotinib because FOLFIRINOX led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group. 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 (8).

S-1, an oral fluoropyrimidine derivative, is now widely used for a variety of malignancies such as gastric cancer (9,10). In Phase II studies of S-1 for metastatic pancreatic cancer, response rates of 21.1–37.5% and median overall survival of 5.6–9.2 months were reported (11,12). Preclinical studies have demonstrated a synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells (13). On the basis of these findings, we decided to investigate combination therapy with gemcitabine and S-1 therapy (GS therapy) for pancreatic cancer. We initially conducted a Phase I study of GS therapy in patients with advanced pancreatic cancer (14). In that study, gemcitabine was administered as a 30-min intravenous infusion on days 1 and 8 along with oral S-1 twice daily from day 1 through day 14, concluding that a gemcitabine dose of 1000 mg/m^2 and an S-1 dose of 40 mg/m^2 twice daily was recommended in future studies. Since GS therapy showed promising activity, with a 33% response rate and a median survival of 7.6 months, the present multicenter Phase II study was conducted in patients with metastatic pancreatic cancer to evaluate the efficacy and toxicity profile of GS therapy.

PATIENTS AND METHODS

Patient Selection

Patients were included if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma of the pancreas; at least one measurable metastatic lesion; no history of prior chemotherapy or radiotherapy for pancreatic cancer; age 20–74 years; Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ functions (leucocyte count, 4000–12 000/mm^3; neutrophil count, $\geq$2000/mm^3; platelet count, $\geq$100 000/mm^3; hemoglobin level, $\geq$9.0 g/dl; serum creatinine level, $\leq$1.5 mg/dl; serum AST and ALT levels, $\leq$150 U/l and serum total bilirubin level, $\leq$2.0 mg/dl or $\leq$3.0 mg/dl if biliary drainage was present).

The exclusion criteria were as follows: symptomatic pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; central nervous system metastasis; active concomitant malignancy; severe mental disorder; serious complications such as active gastrointestinal ulcer or severe diabetes mellitus and pregnancy or lactation. The study was approved by the institutional review board of each participating center, and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research (the Ministry of Health, Labour and Welfare, Japan). Written informed consent was obtained from all patients. This study is registered in the UMIN Clinical Trials Registry with the identifier C000000173.

Treatment

This study was an open-label, multicenter, single-arm Phase II study. The dose schedule of gemcitabine and S-1 was planned based on the results of the previous Phase I study (14): gemcitabine at a dose of 1000 mg/m^2 was administered as a 30-min intravenous infusion weekly for 2 weeks followed by 1 week of rest. Oral S-1 was administered at a dose of 40 mg/m^2 twice daily (80 mg/day for body surface area (BSA) $<$1.25 m^2, 100 mg/day for 1.25 $\leq$ BSA $<$ 1.50 m^2 and 120 mg/day for BSA $\geq$1.50 m^2) from days 1 to 14 followed by a 1 week rest period. The treatment was repeated every 3 weeks until disease progression, unacceptable toxicity or patient refusal.

Prophylactic administration of antiemetic agents such as dexamethasone and/or a 5-HT3 receptor antagonist was allowed at the investigator's discretion. If patients showed a leucocyte count of $<$2000/mm^3 or $>$12 000/mm^3, or a platelet count of $<$70 000/mm^3 during the cycle, administration of both gemcitabine and S-1 was suspended. If patients showed a leucocyte count of $<$3000/mm^3 or $>$12 000/mm^3, platelet count of $<$100 000/mm^3, total bilirubin $>$3.0 mg/dl, AST and ALT levels $>$150 U/l, or a creatinine level $>$1.5 mg/dl, initiation of the next cycle was postponed until recovery. When patients experienced (i) Grade 4 leucopenia or neutropenia, (ii) febrile

neutropenia or infection with Grade 3 leucopenia or neutropenia, (iii) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring transfusion or (iv) ≥Grade 3 non-hematological toxicity excluding anorexia, nausea, vomiting, constipation, fatigue and hyperglycemia, the dose of gemcitabine was reduced to 800 mg/m^2 and the dose of S-1 was reduced by 20 mg/day in the subsequent cycle. The protocol treatment was discontinued if the patients required more than two dose reductions or if the subsequent cycle could not be initiated within 28 days after the final day of the anti-cancer drug administration in the previous cycle.

Evaluation

All the eligible patients who received at least one dose of GS therapy were included in the response and toxicity evaluations. Physical examination, complete blood cell counts and biochemistry tests were assessed at least on days 1 and 8 in each cycle during chemotherapy. Tumor marker carbohydrate antigen (CA) 19-9 was measured every 4–6 weeks. Objective tumor response was evaluated every 4–6 weeks by computed tomography or magnetic resonance imaging according to the Response Evaluation Criteria In Solid Tumors version 1.0. For the purpose of confirmation of objective response, an interval of at least 4 weeks was required for complete response (CR), partial response (PR) and stable disease (SD) in this study. The response duration was defined as the interval from the first documentation of response (PR or CR) to the first documentation of tumor progression. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Progression-free survival (PFS) was calculated from the date of the initiation of treatment until documented disease progression or death due to any cause (whichever occurred first); overall survival was calculated from the date of treatment initiation to the date of death or censored at the last follow-up. An external review committee confirmed objective responses and adverse events.

Statistical analysis

The primary endpoint was the response rate (CR and PR) of GS therapy. Forty-nine patients were required based on the assumption of an expected response rate of 25% and the threshold rate of 10%, with α-error of 2.5% (one-sided) and β-error of 20%. In consideration of ineligible patients or those who dropped out, it was planned that 55 patients would be included in this study. We calculated the response rate with 95% confidence interval (CI) in the patients who met eligibility criteria and received at least one GS therapy. The progression-free and overall survival periods were estimated by the Kaplan–Meier method.

RESULTS

Patients

Fifty-five patients were enrolled from 10 institutions between October 2004 and July 2005. Of these 55 patients, one patient was excluded from analysis because he left the study before administration of GS therapy due to an allergic skin reaction caused by insulin. All of the remaining 54 patients received at least one dose of GS therapy and were included in the evaluation of response and toxicity. Patient characteristics of the 54 patients are listed in Table 1. All patients had metastatic disease and no patient received any prior therapies except surgery for pancreatic cancer. Six patients underwent percutaneous transhepatic or endoscopic biliary drainage for obstructive jaundice prior to the study enrollment.

Treatments

The final data were fixed on 31 March 2007. A total of 425 therapy cycles were administered to the 54 patients,

Table 1. Patient characteristics ($n = 54$)

Characteristics		Number of patients (%)
Median age, years (range)	62 (32–74)	
Sex		
Women		24 (44)
Men		30 (56)
ECOG performance status		
0		38 (70)
1		16 (30)
Body surface area		
Median (range), m^2	1.59 (1.18–1.83)	
History of surgical resection		9 (17)
Metastatic disease		54 (100)
Sites of metastasis		
Liver		50 (93)
Distant lymph nodes		11 (20)
Peritoneum		3 (6)
Lung		2 (4)
Other		2 (4)
Histology		
Adenocarcinoma		53 (98)
Adenosquamous carcinoma		1 (2)
Differentiation		
Well		2 (4)
Moderate		28 (52)
Poor		13 (24)
Unknown		11 (20)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Efficacy results

		Number of patients (%)
Tumor response ($n = 54$)		
Complete response		0 (0)
Partial response		24 (44.4)
Stable disease		26 (48.1)
Progressive disease		2 (3.7)
Cannot be evaluated		2 (3.7)
Response rate (95% CI), %	44.4 (30.9–58.6)	
Tumor control rate (95% CI), %	92.6	
CA 19-9 response ($n = 41$)		
Decreased (≥50%)		35 (85.4)
Decreased (<50%)		3 (7.3)
Increased		3 (7.3)
Progression-free survival ($n = 54$)		
Median (95% CI), months	5.9 (4.1–6.9)	
Overall survival ($n = 54$)		
Median (95% CI), months	10.1 (8.5–10.8)	
1-year survival rate, %	33	

CA 19-9, carbohydrate antigen 19-9.

with a median of 7 cycles each (range, 1–24). GS therapy could generally be administered on an outpatient basis. The gemcitabine on day 8 was administered in 367 (86.4%) of 425 cycles. Dose reduction was required in 30 patients (55.6%), mainly due to leucopenia, neutropenia, rash or gastrointestinal toxicities. At the time of analysis, protocol treatment was discontinued in 52 patients because of disease progression ($n = 30$) or adverse events ($n = 22$). The reasons for discontinuation due to adverse events were the second episode of Grade 4 neutropenia after one dose reduction (11), prolonged myelosuppression (3), anorexia or nausea (4), rash (2), cerebral infarction (1) and cholangitis (1). After discontinuation of GS therapy, 30 patients received gemcitabine-based chemotherapy, 6 patients received other anticancer drugs including irinotecan and the remaining 18 patients received only supportive care.

Efficacy

The efficacy results are shown in Table 2. Of the 54 patients, 2 patients could not be assessed for response since they withdrew their consent due to toxicity before the first response evaluation. Although no CR was observed, a PR was achieved in 24 of 54 patients, resulting in an overall response rate of 44.4% (95% CI: 30.9–58.6%). The median response duration was 5.3 months (range, 2.4–15.6 months). SD was noted in 26 patients (48.1%) and progressive disease (PD) in 2 patients (3.7%). The serum CA 19-9 level was reduced to less than half from baseline values in 35 (85.4%) of the 41 patients whose pretreatment levels were >100 U/ml. The median PFS was 5.9 months (95% CI: 4.1–6.9 months) with a median overall survival of 10.1 months (95% CI: 8.5–10.8 months) and a 1-year survival rate of 33.0% (Fig. 1).

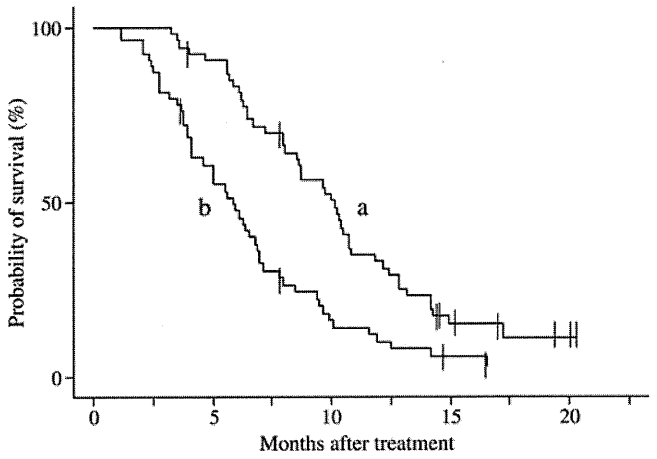

Figure 1. Overall survival curve (a) and progression-free survival (b) for 54 patients.

Toxicity

The major toxicities observed in the 54 patients are listed in Table 3. The most common toxicity was myelosuppression. Grade 3–4 neutropenia and thrombocytopenia occurred in 80 and 22% of the patients, respectively. The neutrophil and platelet count nadirs typically were observed on day 15. Although most of these hematologic toxicities were transient and recovered without serious events, one patient developed Grade 3 febrile neutropenia. No other unexpected severe toxicities were observed during the study and there were no treatment-related deaths. Although gastrointestinal toxicities and skin rash were frequently observed, most of these were manageable with appropriate medical treatment. There were no cumulative toxicities.

DISCUSSION

The major toxicity of GS therapy is myelosuppression, especially neutropenia. Although the incidences of Grade 3–4 neutropenia and thrombocytopenia observed in the current study were high (Table 3), most of these episodes were transient. There was only one episode of neutropenic fever without treatment-related death. Therefore, most patients could be treated on an outpatient basis without receiving granulocyte colony-stimulating factor or a blood transfusion. Although anorexia, nausea, fatigue, rash, pigmentation and aminotransferase elevation were also observed frequently in our study, most of these non-hematological toxicities were manageable with appropriate treatments. Therefore, it is considered that GS therapy in this study is tolerable for patients with metastatic pancreatic cancer.

Table 3. Adverse events ($n = 54$)

	Grade				Grades 1–4	Grades 3–4
	1	2	3	4	%	%
Hematological toxicity						
Leucocytes	3	19	31	1	100	59
Neutrophils	2	9	24	19	100	80
Hemoglobin	11	29	8	0	89	15
Platelets	15	23	12	0	83	22
Non-hematological toxicity						
Bilirubin	15	9	3	0	50	6
AST	23	6	2	0	57	4
ALT	20	11	4	0	65	7
Creatinine	7	0	0	0	13	0
Nausea	19	11	3	—	61	6
Vomiting	11	5	1	0	32	2
Anorexia	18	11	9	0	70	17
Stomatitis	20	10	1	0	57	2
Diarrhea	12	5	0	0	32	0
Constipation	2	0	1	0	6	2
Ileus	—	0	1	0	2	2
Colitis	—	0	1	0	2	2
Fatigue	22	14	3	0	72	6
Fever	15	5	0	0	37	0
Alopecia	13	2	—	—	28	0
Rash	13	17	4	0	63	7
Pigmentation changes	27	7	—	—	63	0
Hand-foot skin reaction	3	0	0	0	6	0
Infection without neutropenia	2	2	2	0	11	4
Febrile neutropenia	—	—	1	0	2	2
CNS cerebrovascular ischemia	—	—	1	1	4	4

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

To date, several Phase II studies testing the gemcitabine plus S-1 combination as first-line therapy for advanced pancreatic cancer have been published (Table 4) (15–18). One study was conducted in Japan and the remaining studies were in Korea. Although various schedules of gemcitabine and S-1 administration were used, the regimens adopted in all studies including this study were similar: gemcitabine at a dose of 1000–1250 mg administered on days 1 and 8 or 8 and 15 and S-1 at a dose of 60–80 mg/m^2/day on days 1–14 of a 21-day cycle. The incidences and severity of toxicities reported in these trials, especially hematological toxicities, have varied widely among the studies. Interestingly, hematological toxicities were more frequently observed in the two Japanese studies, including this study, than the Korean studies. It is well known that the toxicity profile of S-1 differs between Asians and Caucasians (19); Goh and coworkers (20) carried out a study to compare S-1 pharmacokinetics and CYP2A6 activity among Asian and Caucasian patients, and reported that Asian patients had lower 5-FU exposure and lower CYP2A6 activity compared with Caucasian patients. However, the reasons for the discrepancies between the Japanese and Korean studies remain unclear.

In this trial, GS therapy produced a promising efficacy with a response rate of 44.4%. The efficacy of GS therapy reported in the recent studies as well as this study has been consistent (Table 4), with response rates of 27.3–38%, median time to tumor progression of 4.6–5.43 months and median overall survival of 7.89–12.5 months. Recently, the results of a randomized Phase II study comparing GS therapy with gemcitabine alone were reported (21). In that study, 106 patients were randomly assigned at a 1:1 ratio to either the GS group or the gemcitabine-alone group. Patients assigned to GS therapy received gemcitabine at a dose of 1000 mg/m^2 on days 1 and 15 and S-1 at a dose of 40 mg/m^2 twice daily on days 1–14, every 4 weeks. The objective response rate was 18.9% in the GS group and 9.4% in the gemcitabine group. Patients in the GS group demonstrated significantly longer PFS than those in the gemcitabine group [median PFS, 5.4 versus 3.6 months; hazard ratio = 0.64 (95% CI: 0.42–0.97); $P = 0.036$], while overall survival did not differ significantly between the two groups [median

Table 4. Phase II studies of GS therapy for advanced pancreatic cancer

Author	Gemcitabine (mg/m^2)	S-1 (mg/m^2/day)	Cycle (day)	No. of patients	Metastatic disease (%)	RR (%)	Median TTP/PFS (months)	Median OS (months)	Grade 3/4 neutropenia (%)	Grade 3/4 thrombocytopenia (%)
Nakamura *et al.* (15)	1000 (days 8, 15)	60 (days 1–14)	21	33	100	48	5.4	12.5	55	15
Lee *et al.* (16)	1250 (days 1, 8)	80 (days 1–14)	21	32	90.6	44	4.92	7.89	28.1	15.6
Kim *et al.* (17)	1000 (days 8, 15)	60 (days 1–14)	21	22	86.3	27.3	4.6	8.5	18.2	4.5
Oh *et al.* (18)	1000 (days 1, 8)	80 (days 1–14)	21	38	84	29	5.43	8.4	39.5	2.6
Current study	1000 (days 1, 8)	80 (days 1–14)	21	55	100	44.4	5.9	10.1	80	22

RR, response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival.

overall survival, 14.1 versus 8.7 months; hazard ratio = 0.69 (95% CI: 0.43–1.08); $P = 0.105$].

Since it is speculated that combination chemotherapy with S-1 and gemcitabine might be superior to monotherapy with gemcitabine from the results of the recent trials, a Phase III trial was planned to confirm the efficacy of GS therapy (ClinicalTrials.gov, NCT00498225). The Phase III study known as 'GEST' is a randomized controlled study involving three arms: gemcitabine monotherapy as a control arm, S-1 monotherapy and GS therapy. The trial was designed to evaluate overall survival as the primary endpoint, non-inferiority of S-1 to gemcitabine and superiority of GS therapy over gemcitabine. The enrollment of 750 patients was planned and has already been completed and the final analysis of the results will be reported in the near future.

In conclusion, the current Phase II study demonstrated encouraging antitumor activity following GS therapy with good overall survival in patients with metastatic pancreatic cancer. The clinical benefits of GS therapy are now investigated in the GEST trial.

Acknowledgements

We are grateful to Drs T. Kosuge, Y. Matsumura and T. Kodama, who served as an Independent Data Monitoring Committee. We thank Drs Y. Ishiguro, N. Moriyama and M. Nagase for their extramural review. We also thank Ms K. Sato who provided advice on ethics, and Ms Y. Yoshimoto, Ms E. Shiokawa, Ms K. Kondo and Ms. R. Mukouyama for their assistance with data management.

Funding

This work was supported by funding from Health and Labor Sciences Research Grant for Clinical Cancer Research, Ministry of Health, Labor and Welfare, Japan.

Conflict of interest statement

None declared.

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Appendix

In addition to the authors listed in the author field, following are the authors who contributed equally to this study.

Atsushi Makimoto, Division of Pediatrics, National Cancer Center Hospital, Tokyo, Japan.

J Hepatobiliary Pancreat Sci
DOI 10.1007/s00534-011-0495-1

Possibility of immunotherapy for biliary tract cancer: how do we prove efficacy? Introduction to a current ongoing phase I and randomized phase II study to evaluate the efficacy and safety of adding Wilms tumor 1 peptide vaccine to gemcitabine and cisplatin for the treatment of advanced biliary tract cancer (WT-BT trial)

Takuji Okusaka · Makoto Ueno · Tosiya Sato · Yuji Heike

Abstract

Background/purpose In biliary tract cancer, few clinical studies evaluating immunotherapy have been reported. A phase I and randomized phase II study with Wilms tumor 1 (WT1) peptide vaccine plus gemcitabine and cisplatin (GC) for chemo-naïve patients with unresectable or recurrent biliary tract cancer was started, because the overexpression of WT1 is seen in the majority of patients with this disease, encouraging the potential of WT1-based immunotherapy. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000004886.

Methods and results The aim of this trial is to evaluate the efficacy and safety of the regimen and to determine whether the regimen should be compared with the current standard regimen, GC, in a subsequent phase III trial for patients with unresectable or recurrent biliary tract cancer. Six patients in the phase I study and a total of 100 patients in the phase II study will be accrued over a 2-year period. The patients in the phase II study will be randomized at a 2:1 ratio to receive GC either with or without WT1 peptide vaccine. The primary endpoint of the phase II study is the 1-year overall survival rate.

Conclusions This is the first randomized trial to evaluate the use of immunotherapy in patients with advanced biliary tract cancer.

Keywords Biliary tract cancer · Immunotherapy · Chemotherapy · Wilms tumor 1 (WT1) peptide vaccine · Randomized trial

Introduction

Systemic chemotherapy is usually indicated for patients with unresectable advanced biliary tract cancer or for those who have relapsed after operation; however, no standard treatments with solid evidence of a survival benefit have been established for such patients [1]. Although gemcitabine (GEM) alone was regarded as the de-facto standard regimen for advanced biliary cancer until recently, gemcitabine plus cisplatin (GC) has become the new standard regimen, based on the results of the ABC-02 trial [2], which showed a significant survival advantage for the GC combination over GEM alone. Even with the establishment of a standard therapy for this disease, the prognosis of these patients remains dismal: their median survival period is only around 10 months [2, 3]. Therefore, a clear need exists for new, effective, treatments for the management of biliary tract cancer (Fig. 1).

Recent progress in understanding the basic aspects of immunology has led to the development of immune-based therapies for various types of cancers. The identification of

T. Okusaka (✉)
Hepatobiliary and Pancreatic Oncology Division,
National Cancer Center Hospital, 5-1-1 Tsukiji,
Chuo-ku, Tokyo 104-0045, Japan
e-mail: tokusaka@ncc.go.jp

M. Ueno
Division of Hepatobiliary and Pancreatic Medical Oncology,
Kanagawa Cancer Center, Yokohama, Japan

T. Sato
Department of Biostatistics, Kyoto University
School of Public Health, Kyoto, Japan

Y. Heike
Department of Medical Oncology,
National Cancer Center Hospital, Tokyo, Japan

Published online: 25 January 2012

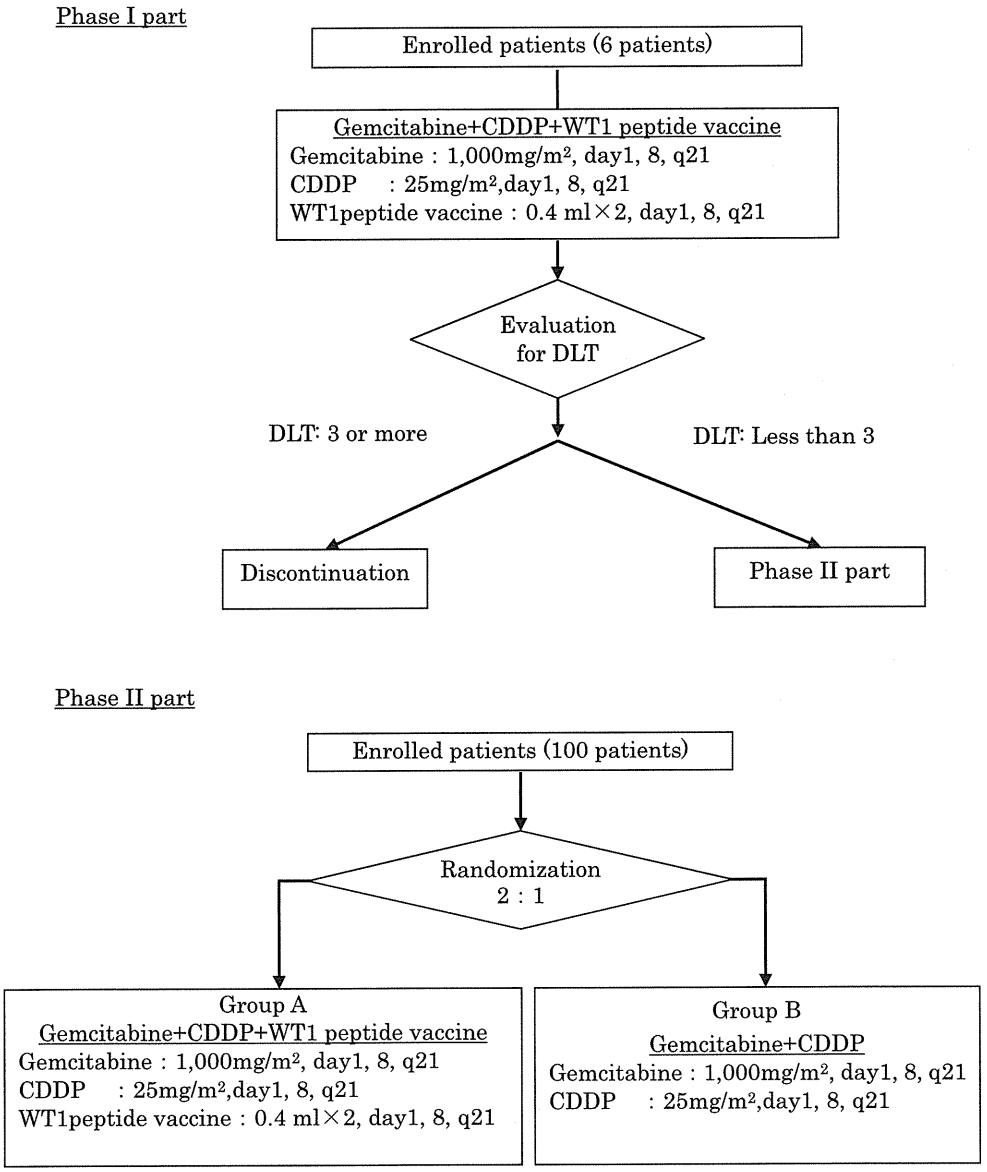

Fig. 1 Study design. *DLT* dose-limiting toxicity, *CDDP* cisplatin, *WT 1* Wilms tumor 1

various cancer antigens has facilitated many clinical trials of cancer vaccines that are expected to become new treatment strategies. Recently, sipuleucel-T immunotherapy for metastatic, asymptomatic hormone-refractory prostate cancer [4] and immunotherapy with ipilimumab for metastatic melanoma [5] have produced statistically significant improvements in survival, and both of these treatments have been approved by the United States Food and Drug Administration. Sipuleucel-T stimulates T-cell immunity against prostatic acid phosphatase, and ipilimumab blocks the potentiation of cytotoxic T-lymphocyte-associated antigen 4 and the antitumor T-cell response. Unfortunately, few preclinical studies examining biliary tract cancer have shown promising immune responses similar to those induced by sipuleucel-T against prostate cancer or those induced by ipilimumab against melanoma, and few clinical studies of immunotherapy for biliary tract cancer have been reported because of the rarity of this disease and the poor physical conditions of most patients at the time of the initial diagnosis. However, GEM has been reported not to suppress immunological cells, but to increase the population of dendritic cells that serve as antigen-presenting cells [6, 7]. Therefore, we conducted a phase I trial of Wilms tumor 1 (WT1) peptide vaccine and GEM combination therapy in patients with advanced pancreatic or biliary tract cancer [8]. Although the aim of that study was to assess the safety of the combination of WT1 peptide vaccine and GEM in a small population, it also showed that the WT1 peptide vaccine was safe enough to be employed in patients with advanced pancreatic or biliary tract cancer in combination with GEM, and

that the efficacy of the combination therapy seemed to be promising, as outlined below.

We recently initiated a phase I and randomized phase II study to evaluate the efficacy and safety of adding the WT1 peptide vaccine to GC in advanced biliary tract cancer (WT-BT trial), since GC has become the new standard and because the WT1 peptide vaccine is an attractive candidate as a partner for chemotherapy to improve survival in patients with advanced biliary tract cancer. WT1 protein is overexpressed in various types of cancer cells, including biliary tract cancer cells [9], and it was ranked as the No. 1 antigen in the cancer antigen prioritization project of the National Cancer Institute [10].

To our knowledge, this is the first randomized clinical trial to evaluate immunotherapy for biliary tract cancer. The study complied with the Declaration of Helsinki. Informed consent was obtained from all the patients, and the protocol was approved by the ethics committees at all participating institutions. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000004886 (http://www.umin.ac.jp/ctr/index.htm). The study was initiated in January 2011.

1. The results of a phase I trial of WT1 peptide vaccine and GEM combination therapy in patients with advanced pancreatic or biliary tract cancer

An open-labeled, dose-escalation phase 1 trial of WT1 vaccine and GEM combination therapy for patients with advanced pancreatic cancer or biliary tract cancer was performed. The primary endpoint was the evaluation of the toxicity, safety, and optimal immunological dose of the vaccine. Human leukocyte antigen (HLA)-A 0201, HLA-A 0206, and/or HLA-A 2402-positive patients with inoperable advanced pancreatic or biliary tract cancer who had not previously been treated with GEM were eligible for this study. Six doses of GEM and 4 doses of WT1 peptide (1 or 3 mg) emulsified in Montanide adjuvant were administered over 2 months. Twenty-five patients (13 male and 12 female) were enrolled. Nine patients had inoperable advanced pancreatic cancer, 8 had gallbladder cancer, 4 had intrahepatic, and 4 had extrahepatic bile duct cancer. The adverse events were comparable to those seen with GEM alone. Delayed-type hypersensitivity test was positive after vaccination in 2 patients, and WT1-specific T cells in peptide-stimulated culture were detected by tetramer assay in 59% (13 of 22) of the patients. The disease control rate at 2 months was 89% for pancreatic cancer and 50% for biliary tract cancer. With a median follow-up time of 259 days, the median survival time for patients with biliary tract cancer was 288 days, and that for patients with pancreatic cancer was 259 days. Although objective clinical efficacy was not apparent, the safety of the WT1 vaccine and GEM combination therapy was confirmed in this study.

2. An ongoing phase I and randomized phase II study to evaluate the efficacy and safety of adding WT1 peptide vaccine to GC in advanced biliary tract cancer (WT-BT trial).

Protocol summary of the WT-BT trial

Study setting

The study is a multi-institutional open-label phase I and randomized phase II trial.

Objectives and endpoints

The aim of this phase I/II study is to determine the recommended dosage of WT1 peptide vaccine when used in combination with GC chemotherapy and to clarify the safety and efficacy of GC plus WT1 peptide vaccine when administered at the recommended dose, in comparison with GC alone.

In the phase I study, we will investigate the frequency of the dose-limiting toxicity (DLT). The criteria for a DLT will include: Grade 4 neutropenia for 8 or more consecutive days, Grade 3 neutropenia accompanied by a fever ($\geq$37.5°C), Grade 4 thrombocytopenia or the need for a transfusion, a Grade 4 aspartate transaminase (AST)/alanine transaminase (ALT) elevation or a Grade 3 AST/ALT elevation for 8 or more consecutive days, Grade 3 or 4 nonhematological toxicity (except for rash, hyperglycemia, gamma-GTP elevation, and any temporary events not affecting the protocol treatment), Grade 3 or 4 local skin inflammation at the vaccine injection sites, or Grade 1 or greater interstitial pneumonia.

In the phase II study, the primary endpoint will be the 1-year overall survival rate for all eligible patients. Overall survival will be defined as the number of days from randomization until death from any cause, and the data will be censored as of the last follow-up day on which the patient was alive. The secondary endpoints will be progression-free survival, response rate, median survival time, 2-year overall survival rate, percentage of adverse events, percentage of serious adverse events, and immunological responses (multimer assay and delayed-type hypersensitivity).

Eligibility criteria

Inclusion criteria

For inclusion in the study, patients are required to fulfill all the following criteria:

1. Clinically diagnosed with biliary tract cancer, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer.
2. Recurrent or unresectable biliary tract cancer.
3. Histologically proven papillary adenocarcinoma, tubular adenocarcinoma, or adenosquamous carcinoma for patients with extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer; histologically proven adenocarcinoma for patients with intrahepatic cholangiocarcinoma.
4. Without central nervous system metastasis.
5. Without moderate or greater ascites/pleural effusion.
6. No previous therapy for biliary tract cancer.
7. No previous operation, chemotherapy, or radiotherapy for any other malignancies within the past 5 years.
8. No previous chemotherapy containing gemcitabine or cisplatin for any other malignancies.
9. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Sufficient oral intake.
11. Age of 20–80 years.
12. Adequate organ functions.
13. HLA of A2402, A0201, or A0206.
14. Written informed consent.

Exclusion criteria

Patients will be excluded if they meet any of the following criteria:

1. Simultaneous or metachronous (within the past 5 years) double cancers, with the exception of intramucosal tumors curable with local therapy.
2. Pregnant or lactating women or women of childbearing potential and men who wish to father children.
3. Psychosis.
4. Patients requiring systemic steroid medication.
5. Interstitial pneumonia or fibroid lung disease.
6. Active bacterial or fungous infection.
7. Severe complications.
8. Drug allergies to drugs containing iodine compounds and/or gadolinium.
9. Inadequate physical condition, as diagnosed by the primary physician.

Randomization in the phase II study

After the fulfillment of the eligibility criteria has been confirmed, patient registration for both the phase I and II studies will be made by faxing the Data Center. Eligible patients in the phase II study will be stratified according to HLA (A2402/A02XX) and then randomized at the Data Center at a 2:1 ratio, using a minimization method and balancing the study arms according to institution, primary tumor (gallbladder cancer/other than gallbladder cancer), and history of surgical resection for the primary tumor (recurrent/advanced) to receive GC either with or without the WT1 peptide vaccine.

Treatment methods

For the patients in the phase I study, the GC and WT1 vaccine will be administered according to the following schedule: cisplatin (25 mg per m^2 of body-surface area) followed by gemcitabine (1000 mg per m^2) administered intravenously on days 1 and 8 every 3 weeks, with the vaccine (3 mg per body) injected subcutaneously alternating between 2 areas on the unilateral axillary fossa and inguen on days 1 and 8.

For both arms in the phase II study, GC will be administered according to the same dose and schedule as those used in the phase I study, but the vaccine will be administered only for the GC plus WT1 peptide vaccine arm.

The protocol treatments will be continued until disease progression, unacceptable toxicity, or patient refusal, although cisplatin will be continued for only a maximum of 24 weeks.

Follow-up

Enhanced abdominal computed tomography (CT)/magnetic resonance imaging, chest CT/X-rays, and tumor marker levels (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA] 19-9) will be evaluated at least every 6 weeks during the protocol treatment. Patients will be seen on days 1 and 8 of every cycle for a physical examination to monitor their symptoms and the possible toxic effects of treatment. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Study design and statistical analysis

In the phase I study, six patients will be recruited to determine whether a WT1 peptide vaccine dose of 3 mg per body can be recommended for use in combination with GC. A dose of 3 mg per body is the recommended dose for the WT1 peptide vaccine when used in combination with GEM alone, as determined in the previous phase I study. If treatment-related DLTs occur in no more than two of the six patients, transition to the phase II study will be

permissible with the approval of the independent data monitoring committee. If DLTs occur in three or more patients, transition to the phase II study will be terminated.

In the phase II study, 100 patients will be allocated to either of the two arms to evaluate the safety and efficacy of GC plus WT1 peptide vaccine, in comparison with GC alone. The sample size was determined based on the feasibility of the study after considering the research period, the number of participating institutions, and the available financial resources. A total of 66 patients in the GC plus WT1 peptide vaccine arm would enable the 1-year overall survival rate to be estimated with an accuracy of ±10%.

Interim analysis and monitoring

We do not plan to perform an interim analysis in this study. In-house monitoring will be performed every 6 months by the Data Center to evaluate the study progress and to improve the quality of the study.

Discussion

So far, no consensus exists regarding the "best criteria" for evaluating the effectiveness of cancer immunotherapy. Evidence of therapeutic activity may be difficult to obtain in early-phase trials using standard endpoints such as the antitumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST), because most cancer immunotherapies are not expected to result in notable tumor shrinkage. Recently published FDA guidance suggests that the development of a cancer vaccine may present different considerations for clinical trial design than the development of a traditional cytotoxic drug or biological product for the treatment of cancer (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

We retrieved clinical trials using immunotherapy for biliary tract cancer through PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and ClinicalTrial.gov (http://clinicaltrials.gov/), although no reports or ongoing studies were found in this category, except for two trials: our previous phase I study examining GEM plus the WT1 peptide vaccine [8], and another study (phase II) examining chemoradioimmunotherapy, with interleukin 2 and 13-cis-retinoic acid being used for the immunotherapy [11]. Both studies conducted for pancreatic or biliary tract cancer showed some promise for a survival advantage, although the reported evidence was immature. We initiated the current phase I and randomized phase II studies to evaluate the efficacy and safety of adding the WT1 peptide vaccine to GC for the treatment of advanced biliary tract cancer. These studies are only the initial step in the development of immunotherapy for this disease, although we hope that the trial may provide useful data for assessing the true activities of this treatment.

Acknowledgments The authors thank Professor Yasuo Ohashi for his marked support as the director of the Data Center and Dr. Keiko Sato for her advice on ethics and for the preparation of the informed consent form. This study is supported by the Labour Sciences Research Grant for Clinical Cancer Research (H22-Ganrinsho-Ippan-013) from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest None.

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臨床試験論文の読み方

手良向　聡

臨 床 血 液　第52巻第10号 別刷
(2011年10月)

第73回日本血液学会学術集会
教育講演 B-7
基礎シリーズ

臨床試験論文の読み方

手良向 聡

Key words : Clinical trial design, Statistical hypothesis, Endpoint, Randomization

1. はじめに

臨床試験の論文を正しく読むためには，臨床試験の方法論，すなわち臨床試験の計画から結果の解釈までの一連の方法の体系について知る必要がある。本稿では，臨床試験，主にランダム化対照試験（RCT: randomized controlled trial）の標準的方法論について述べる。

2. 医学・医療と技術評価

一般に，医学は普遍性のある真実を追求する科学の一分野である一方，医療は多様性のある個人に対して最適な技術を選択して適用することが要求される場である。技術評価は，主に統計学に基づく科学的方法を駆使して医療技術を相対的に評価し，医学から医療への橋渡しを行う（図1）。

統計学を医学・医療の領域に導入する際には，2つの大きなギャップを認識しておく必要がある。1つは，「決定論」と「非決定論（確率論）」のギャップである。1800年代半ばにクロード・ベルナールが「統計学に立脚している限り，医学は永久に推測科学に止まるであろう」と決定論的な考え方を主張して以来，医学の世界では決定論的な思想が支配的である。もう1つのギャップは，意思決定の主体に関わる問題であり，「対集団の確率」と「対個人の確率」とのギャップである。たとえば，ある医薬品を承認すべきかどうかという判断は，その国の人々という集団に対するベネフィットとリスクのバランスで決定される。その決定は「対集団の確率」に基づく。一方，医療の場で診断や治療を行う際には，個人に対するベネフィットとリスクを評価しなければならない。たとえば，胎児診断を行って，医師が「胎児に異常がある確率は80%」と言ったとき，その80%は集団での頻度であり，この確率は確信度を量的に表現したものである。しかしながら，それを聞いた母親の「子供には異常があるか（100%），ないか（0%）のどちらか」という感覚では，この集団での確率を抵抗なく受け入れられない。このような確率に関する認識のギャップを認識しないで，道具としての統計学だけを医学・医療の領域に導入することは非常に危険である[1]。

臨床試験は，20世紀を代表する英国の統計学者R.A.フィッシャー（1890～1962）が創始した統計的実験（技術的実験とも呼ばれる）の方法論を基礎としている。科学的実験は，人工的に作り出された純粋な条件のもとでの因果関係を確定しようとするのに対して，統計的実験は以下の特徴を有する[2]。

- 実験の場は，現実の応用の場に近い状況に設定される
- 結果の分析には誤差の存在を前提にしなければならない
- いくつかの因子を同時に変化させて結果を見る必要があることがある
- 目的は，何らかの基準によって現実の場において最も良い結果が得られるような条件を求めることである

つまり，臨床試験のプロセス全体―計画を立て，データを収集し，検証・推測を行う―を保証するためには統計的な方法が不可欠である。特に，再現性によって結果を保証することが可能な基礎実験と異なり，同じデザインで繰り返すことが困難な臨床試験においては，プロセスの妥当性から結果を保証するしかない。

3. 臨床試験デザイン

臨床試験に携わる統計家（試験統計家）の役割は，「臨床試験に統計的原則が適切に適用されていることを，臨床試験に携わる他の専門家と共同して保証すること」で

京都大学医学部附属病院 探索医療センター検証部

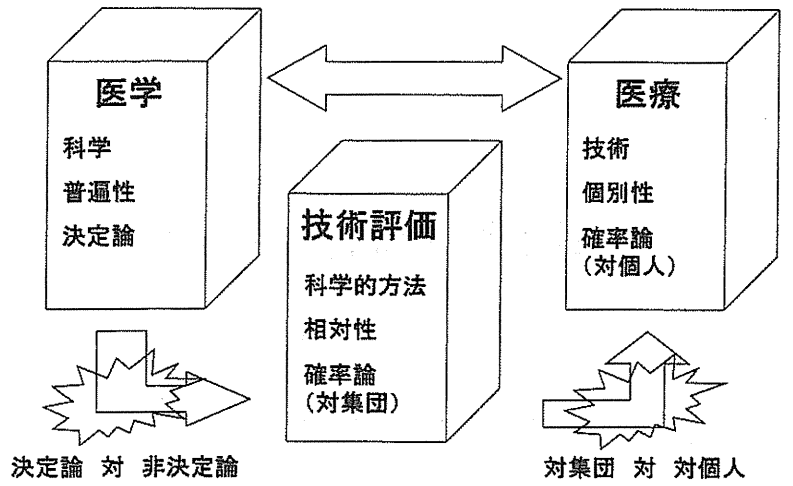

図1 医学・医療と技術評価

ある[3]。臨床試験の性格は検証的試験と探索的試験の2つに大きく分類される。検証的試験とは，事前に定めた仮説を検証するための試験，探索的試験とは検証的でない試験である。しかし実際には，いかなる試験も検証的な側面と探索的な側面の両方を持っており，ある技術を最初にヒトに適用するような試験は探索的な側面が強く，ランダム化対照試験は検証的な側面が強い。重要なことは，試験実施計画書（以下，プロトコル）の作成段階で，それらを区別しておくことである。プロトコルに予定された解析の結果のみが検証的であるとみなされる[3]。一般に，臨床試験を実施する企業や研究者は，得られたデータを様々な手法や様々な部分集団で解析したい誘惑に駆られる。しかしながら，事前に計画していなかった解析から得られた結果を強調しすぎると，消費者リスク（効果のない医療技術が使用されるリスク）—統計的には第Ⅰ種の過誤確率—が増大する。消費者リスクを保証することは，検定の有意水準をある小さな値（例えば，0.05）に設定することに対応している。

プロトコルの核となるのは，「背景と根拠」，「目的」，「対象（適格規準）」，「治療計画」，「エンドポイント（評価項目）」である。これらすべてが確定した段階で，試験統計家が中心となり「試験デザイン」の検討に入る。試験デザインとは，以下を含む。

- 対照の選択…無対照，用量対照，プラセボ対照など
- 統計的仮説…優越性仮説，非劣性仮説など
- 比較の様式…並行群間比較，クロスオーバー，用量漸増など
- ランダム化の有無
- 盲検化の有無
- 中間モニタリングの有無と方法
- 目標症例数の設定

なお，プロトコルに記載すべき項目とその作成要領については，京都大学医学部附属病院 探索医療センター検証部のHP（http://www.kutrc.org）あるいは先端医療振興財団 臨床研究情報センターのHP（http://www.tri-kobe.org）を参照されたい。

4. エンドポイント

エンドポイントとは，「試験の目的に関連する仮説を検証するうえで臨床的に意味があり，客観的に評価できる観察・検査項目またはそれらの合成指標」と定義される。例えば，癌の臨床試験の場合，全生存期間，無病生存期間，無増悪生存期間，腫瘍反応などが代表的なエンドポイントである[4]。全生存期間—ある時点からあらゆる原因による死亡までの時間—は，臨床的に最も適切と考えられているが，患者の長期追跡が必要であることや再発・増悪後の治療に影響を受けることなどの欠点を有する。また，QOL（quality of life）は患者の利益を直接的に表す指標であるが，測定の妥当性・信頼性の問題や複雑な統計解析手法が必要になるという短所を持つ（表1）。その臨床試験で評価すべき最も重要な1つのエンドポイントを主要エンドポイント，それ以外を副次エンドポイントと区別し，主要エンドポイントに対して次項で述べる統計的仮説が設定され，それに基づいて目標症例数が計算される。

臨床試験のエンドポイントを変数の型で分類すると，連続型（例：臨床検査値の推移），二値分類型（例：改善の有無，腫瘍反応の有無），順序分類型（例：改善度—かなり改善，改善，不変，悪化），時間—イベント型（例：全生存期間）の4つに大きく分けられる。エンドポイントの定義を事前にプロトコルに明記することは重要である。特に時間—イベント型の場合，その起点と終点，および打ち切り—ある時点までイベントを発生していない状態で観察を打ち切られること—を詳細に定義し