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A prospective randomized controlled trial of internal versus external drainage with pancreaticojejunostomy for pancreaticoduodenectomy

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KEYWORDS:
Randomized controlled trial;
Stent;
Pancreaticojejunostomy;
Pancreaticoduodenectomy;
Pancreatic fistula;
Complications

Abstract

BACKGROUND: A stent often is placed across the pancreaticojejunostomy. However, there is no report compared between internal drainage and external drainage.

METHODS: We conducted a prospective randomized trial (NCT00628186 registered at http://ClinicalTrials.gov) with 100 patients who underwent pancreaticoduodenectomy and we compared the effects on postoperative course.

RESULTS: The incidence of pancreatic fistula according to the International Study Group on Pancreatic Fistula criteria was not different (external, 20%; vs internal, 26%), and the incidence of the other complications was similar between stent types. The median postoperative hospital stay was 21 days (range, 8–163 d) in the internal drainage group, which was shorter than the median stay of 24 days (range, 21–88 d) in the external drainage group ($P = .016$).

CONCLUSIONS: Both internal drainage and external drainage were safety devices for pancreaticojejunostomy. Internal drainage simplifies postoperative managements and it might shorten postoperative stay for pancreaticoduodenectomy.

Pancreaticoduodenectomy is an aggressive surgery associated with pancreatic fistula, delayed gastric emptying (DGE), and postoperative mortality. Recently, the mortality rate declined to less than 5% at high-volume centers.[1–7] Pancreatic fistula in particular is a severe complication of pancreaticoduodenectomy and may cause intra-abdominal hemorrhage, intra-abdominal abscess, and postoperative mortality by autolytic activity of pancreatic juice. Despite recent progress in surgical techniques and perioperative management, leakage of the pancreaticoenterostomy after pancreatic head resection occurs in some patients.[8]

Duct-to-mucosa anastomosis (DMA) is a 2-layer anastomosis that is intended to prevent pancreatic fistula.[1,2,9,10] In addition, it has been shown that DMA maintains the diameter of the remnant pancreatic duct, which suggests maintenance of exocrine function,[9] whereas an invagination technique also is efficacious pancreaticojejunostomy.[6] Many surgeons have used a stent across the pancreaticojejunostomy to prevent pancreatic fistula, and a stent may be useful for diversion of pancreatic juice from the pancreatic anastomotic site, decompression of the remnant, and patency of the main pancreatic duct. An external drainage tube

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may be placed into the main pancreatic duct and across the pancreaticojejunostomy to divert pancreatic juice.[11] Howard[12] reported no pancreatic fistulas in 56 consecutive cases using the external drainage tube, and a prospective study found that pancreatic fistula decreased from 29% to 7% using an external drainage tube.[13] In a randomized controlled trial (RCT), Poon et al[14] found that patients with an external drainage tube had a significantly lower pancreatic fistula rate compared with a nonstented group, and pancreatic texture did not affect the incidence of pancreatic fistula. By contrast, another RCT showed that pancreatic duct stenting did not decrease the occurrence of pancreatic fistulas in patients who underwent pancreaticoduodenectomy, compared with nonstented patients.[15] These results suggest that an internal pancreatic duct stent does not decrease the frequency of pancreatic fistulas. However, differences in stent type might affect the incidence of pancreatic fistulas. There is no RCT on comparison of stent type.

In this report, we show that internal drainage is useful for postoperative management after pancreaticoduodenectomy.

Methods

Protocol

This RCT was approved by the Ethical Committee on Clinical Investigation of Wakayama Medical University Hospital (WMUH) in February 2005 and was registered at http://ClinicalTrials.gov (NCT00628186). Patients were recruited into this study before surgery, on the basis of whether pancreatic head resection was anticipated at WMUH for pancreatic head and periampullary disease, and appropriate informed consent was obtained. Excluded from the study were the following: (1) patients with severe associated diseases (severe cirrhosis, severe pulmonary disorder, severe cardiac disorder, severe renal failure, hemodialysis, psychologic disorders) that might prolong hospital stay, (2) patients whose conditions were diagnosed inadequately for this study by a physician, (3) patients who could not have a pancreatic stent placed, and (4) patients who did not give informed consent.

Assignment

Before reconstruction after pancreatic head resection, patients were randomized to receive either external drainage (external drainage of the pancreatic duct with a long tube) or internal drainage (internal drainage to the jejunum with a short tube) during the surgery (Fig. 1). A research physician at WMUH conducted the randomization using a computer-generated random number pattern in a central registry for the study.

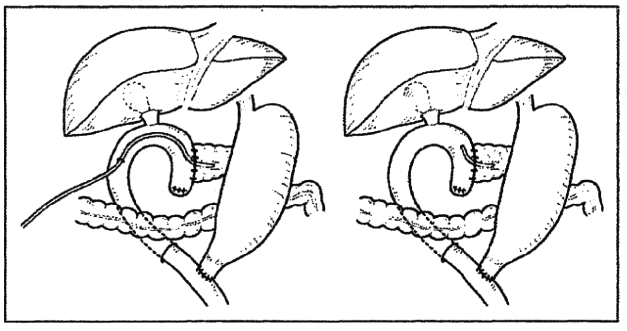

Figure 1 Reconstruction in pylorus-preserving pancreaticoduodenectomy. (Left) Pancreaticojejunostomy using a long stent tube (external drainage). (Right) Pancreaticojejunostomy using a short stent tube (internal drainage).

Procedures and postoperative management

At the time of pancreatic head resection, we removed the gallbladder, distal common bile duct, head of the pancreas, duodenum, and 10 cm of the proximal jejunum. In pylorus-preserving pancreaticoduodenectomy, the proximal duodenum was preserved carefully to include 3 cm distal to the pylorus ring. In pylorus-resecting pancreaticoduodenectomy, the whole stomach was preserved and the pyloric ring was resected on the oral side. The right gastric artery was divided along with the pyloric branch of the vagal nerve. In patients with malignant disease, the following areas of lymph nodes were removed: hepatoduodenal ligament, circumferentially around the common hepatic artery, and the right-half circumference of the superior mesenteric artery.

Pancreaticojejunostomy was performed with DMA in all patients as described previously.[9] An inner mucosal anastomosis was performed between the pancreatic duct and the jejunal mucosa using 8 interrupted 5-0 PDS-II sutures (polydioxanone; Ethicon, Inc, Somerville, NJ), regardless of duct size. Knots in the anterior wall were outside the new lumen, and knots in the posterior wall were inside the lumen. The outer layer of the end-to-side pancreaticojejunostomy was constructed using 4-0 Vascufil (polybutester; Covidien, Co., Glasgow, UK) between the pancreatic tissue and the jejunal serosa to form a seromuscular envelope. The external drainage tube (5F polyethylene pancreatic drainage tube with a small knob; Akita Sumitomo Bake, Co., Akita, Japan) was inserted and exteriorized through the jejunal limb. The internal drainage tube was cut to a length of 5 cm and placed. Both stents were inserted 2.5 cm into the pancreatic duct. A 1-layer hepaticojejunostomy was constructed using interrupted 5-0 PDS-II sutures without a stent. The gastrojejunostomy/duodenojejunostomy was performed by a 2-layer anastomosis (4-0 PDS-II and 3-0 silk) via an antecolic route.[16] One closed-suction drain was placed around the pancreaticojejunostomy. A 16F nasogastric tube was inserted, and this nasogastric tube was removed from all patients on postoperative day 1.

Postoperatively, an intravenous H_2 blocker (famotidine [20 mg/day]; Astellas Pharma, Inc, Tokyo, Japan)

was administered to all patients for 2 weeks. None of the patients was given somatostatin analogues or prokinetic agents such as erythromycin.

The intra-abdominal drain was removed routinely on the fourth postoperative day, however, removal of a drain tube was postponed until normalization of drainage fluid when bile or bowel juice was drained through a postoperative drain.[8] The external drainage tube for the pancreaticojejunostomy was removed on the 21st postoperative day because absorption of the PDS-II sutures fixing the external drainage tube required more than 21 days.

Data collection

Data were collected prospectively from all patients: a history and a pathologic examination were performed, postoperative clinical information was obtained, and complications were noted.

Discharge criteria

Patients were discharged when they fulfilled all the following conditions: a return to preoperative activities of daily living, no deep-site infections, normal laboratory data, no drains, and the possibility for oral nutrition above the basal metabolism.

Study end points

The primary end point was postoperative hospital stay. Secondary end points were mortality and morbidity, including pancreatic fistula, DGE, intra-abdominal hemorrhage, and intra-abdominal abscess. Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula (ISGPF) criteria: the presence of amylase-rich fluid (more than 3-fold higher than the upper limit of normal for serum amylase) of any measurable volume on the third postoperative day.[17] Intra-abdominal abscess was defined as any fluid detected by computed tomography or ultrasonography that required drainage. Pancreatic texture was categorized as hard or soft. A main pancreatic duct of more than 3 mm or the existence of histologic fibrosis was considered to indicate a hard pancreas.

The definition of DGE and intra-abdominal bleeding was followed by ISGPS criterias.[18,19]

Statistical analyses

The study design for predicting the number of patients necessary for statistical validity (2-sided) was based on the premise that postoperative hospital stay would be decreased from 28 to 23 days, with the α value set at .05 and the β value set at .2, yielding a power of 80%. We calculated that 47 patients were required in each arm of this study, for a total study population of 94 patients by unpaired t test. We planned to recruit 50 patients per group, assuming drop-out of some entered patients. Comparisons between the 2 groups were performed using the Mann–Whitney U test for continuous data and the 2-tailed chi-squared test, or the Fisher exact test where appropriate, for categoric data. Results are reported as medians (ranges). The analyses used the Statistical Package for Social Science for Windows (version 15.0; SPSS, Chicago, IL). All statistical tests were 2-sided. Significance was defined as a P value of less than .05. An interim analysis using the Bonferroni method was planned, to be calculated with 50 patients per arm.

Results

Between April 2005 and August 2007 at WMUH, 115 patients underwent pancreatic head resection for benign and malignant disease located in the pancreatic head and periampullary region. One hundred of these patients were enrolled in the study. Specific exclusion criteria included the following: pancreatic duct diameter too small to allow stent placement (n = 4), large pancreatic duct diameter (>10 mm; n = 4), severe cirrhosis (n = 1), severe renal failure (n = 1), hemodialysis (n = 1), psychological disorders (n = 1), and absence of informed consent (n = 3). A consort flow diagram of this RCT is shown in Fig. 2.

Patient characteristics are listed in Table 1. There were no significant differences with regard to age, sex, procedures performed, disease, or perioperative findings between the 2 groups. Of all patients, 11 patients underwent portal vein resection to achieve negative resection margins, and a splenectomy was performed for idiopathic portal hypertension.

Postoperative outcomes are shown in Table 2. The incidence of pancreatic fistula by ISGPF criteria showed no significant difference between the external and internal drainage groups, and that of pancreatic fistula classified as either grade B or C was 6% in both the external drainage group and the internal drainage group, showing no difference between the external and the internal drainage groups. In addition, regardless of the pancreatic texture, the incidence of pancreatic fistula had no significant difference between the external drainage group and the internal drainage group (Table 3). DGE occurred in 8 study patients (8%), and DGE classified as grade B and C was 6% in both the external drainage group and the internal drainage group. Intra-abdominal bleeding was 2% in both the external drainage group and the internal drainage group, and only an internal drainage patient had a complication of intra-abdominal bleeding involved in pancreatic fistula. Neither morbidity nor mortality differed significantly between the external drainage group and the internal drainage group. Of the patients with an external drainage tube, subcutaneous abscess occurred after removal of the external drainage tube at the penetration site of the tube. An 81-year-old patient with an external drainage tube removed the tube herself on the sixth postoperative day, and an intra-abdominal abscess

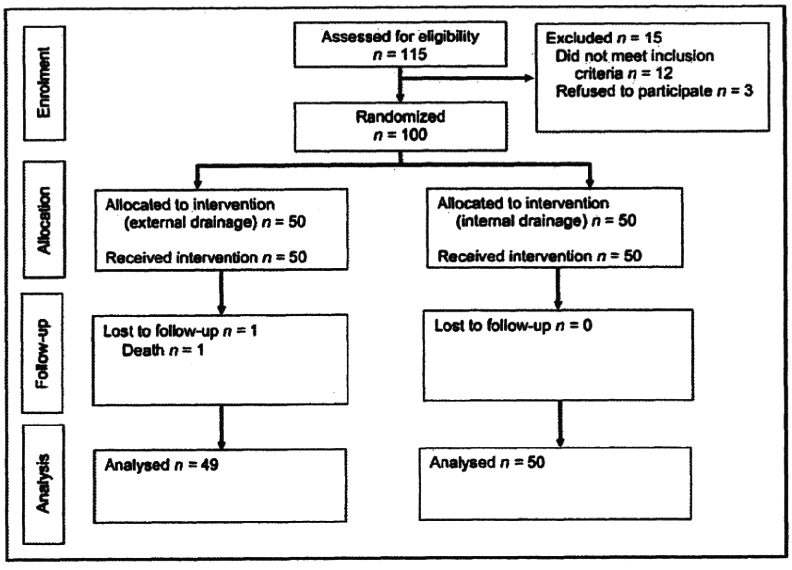

Figure 2 Consolidated Standards of Reporting Trials flow diagram.

developed. The median postoperative hospital stay was 21 days (range, 8–163 d) in the internal drainage group, which was significantly shorter than the median stay of 24 days (range, 21–88 d) in the external drainage group ($P = .016$). Of the internal drainage group, 28 patients showed the hospital stay within 22nd postoperative day, compared with 13 patients from the external drainage group ($P = .003$).

Table 4 shows the postoperative status. On the 14th postoperative day, a median of 75 mL of pancreatic juice (range, 0–500 mL) drained through the external drainage tube. The internal drainage tube fell down to the intestine within 3 months in 35 patients (70%), and within 6 months in 44 patients (88%); only 1 patient retained an internal stent placed at pancreaticojejunostomy 15 months after a pylorus-preserving pancreaticoduodenectomy, and the internal stent fell down at postoperative month 16.

With the exception of 7 patients (1 patient died in the hospital; 2 died from cancer recurrence, and 4 died from

Table 1 Patient characteristics

	External drainage* (n = 50)	Internal drainage† (n = 50)	*P* value
Age, y	70 (44–87)	68 (35–84)	NS
Sex, male/female	28/22	27/23	NS
PpPD/PrPD/PD	16/21/13	22/21/7	NS
Portal vein resection	4	7	NS
Pancreatic texture, hard/soft	35/15	28/22	NS
Preoperative biliary drainage	12	11	NS
Percutaneous/endoscopic	9/3	7/4	NS
Surgical time, min	341 (229–609)	342 (255–559)	NS
Blood loss, mL	745 (120–5620)	763 (45–2665)	NS
Blood transfusion, yes/no	21/29	17/33	NS
Diagnosis			NS
Pancreatic carcinoma	19	23	
Distal bile duct carcinoma	11	8	
Ampullary carcinoma	4	5	
Duodenal carcinoma	1	2	
Pancreatic endocrine tumor	0	1	
Metastatic pancreatic cancer	1	0	
IPMN	12	6	
Mass-forming pancreatitis	2	5	

Patient characteristics had no significant differences between the external drainage group and the internal drainage group. Values are given as median (range) or *n*.

IPMN = intraductal papillary mucinous neoplasm; NS = not significant; PD = pancreaticoduodenectomy; PpPD = pylorus-preserving pancreaticoduodenectomy; PrPD = pylorus-resecting pancreaticoduodenectomy.

*External drainage using long tube.

†Internal drainage using short tube.

Table 2 Postoperative outcome

Complication	External drainage (n = 50) No. (%)	Internal drainage (n = 50) No. (%)	*P* value
Pancreatic fistula	10 (20)	13 (26)	NS
Grade A	7 (14)	10 (20)	NS
Grade B	2 (4)	2 (4)	NS
Grade C	1 (2)	1 (2)	NS
Delayed gastric emptying	4 (8)	4 (8)	NS
Grade A	1 (2)	1 (2)	NS
Grade B	1 (2)	0 (0)	NS
Grade C	2 (4)	3 (6)	NS
Intra-abdominal bleeding	1 (2)	1 (2)	NS
Grade A	0 (0)	0 (0)	NS
Grade B	0 (0)	1 (2)	NS
Grade C	1 (2)	0 (0)	NS
Intra-abdominal abscess	4 (8)	5 (10)	NS
Bile leakage	2 (4)	1 (2)	NS
Liver abscess	1 (2)	3 (6)	NS
Bowel obstruction	3 (6)	1 (2)	NS
Wound infection	1 (2)	4 (8)	NS
Respiratory insufficiency	2 (4)	3 (6)	NS
Sepsis	0 (0)	2 (4)	NS
Gastrointestinal bleeding	1 (2)	1 (2)	NS
ICU readmission	2 (4)	0 (0)	NS
Reoperation	0 (0)	0 (0)	NS
Morbidity	27 (54)	20 (40)	NS
Mortality	1 (2)	0 (0)	NS
Postoperative hospital stay, d*	24 (21–88)	21 (8–163)	.016

Although the incidence of postoperative complications showed no significant difference between the external drainage group and the internal drainage group, only postoperative hospital stay in the internal drainage group was shorter than that in the external drainage group.

ICU = intensive care unit; NS = not significant.

*Median (range).

other causes including cardiovascular disease and traffic accident), 93 patients were observed postoperatively over more than 6 months. Diarrhea, dilatation of the remnant pancreatic duct, and body weight gain were determined 6 months after surgery. No patients had severe diarrhea (grade 3 or 4 according to National Cancer Institute Common Toxicity Criteria, version 3). A patient who had undergone external drainage showed dilatation of the remnant pancreatic duct and pancreatitis. There were no significant differences in fasting blood sugar and hemoglobin A1c levels at postoperative month 6 between the 2 groups.

Comments

In our study, the incidence of postoperative complications showed no significant differences between internal drainage and external drainage after pancreaticoduodenectomy. Although it was difficult to find a difference in the complications including pancreatic fistula, complications should translate to a prolonged postoperative hospital stay.[16,20,21] A shorter postoperative length of hospital stay is considered a predictor of less-invasive surgical procedures and quicker resumption of activities of daily living among patients after pancreaticoduodenectomy. If internal drainage has an advantage over external drainage, it was the reduced length of hospital stay, and a shorter hospital stay may become a barometer of less-invasive surgery. Comparing lengths of postoperative hospital stay in Japan is difficult because the Japanese health care system is different from the health care systems of the Western world. Therefore, we created objective criteria for discharge, and patients were discharged only when they fulfilled the criteria.

Pancreatic fistula is a specific complication of pancreatic head resection and also contributes to postoperative mortality.[22,23] In particular, a soft pancreas is the most remarkable risk factor for pancreatic fistula because a soft pancreas is fragile and secretes a high amount of pancreatic juice.[9,10,24,25] However, the different definitions of pancreatic fistula have hindered comparisons of the incidence of pancreatic fistula. The ISGPF proposed a grading system for a universal definition,[17] and it has been reported that a grade A pancreatic fistula is a transient pancreatic fistula and has no impact on postoperative course.[21] The present study showed that the incidence of both pancreatic fistula in general and pancreatic fistula classified as either grade B or C did not differ significantly between patients with external drainage and those with internal drainage. Indeed, placement of an external drainage tube had a significantly lower pancreatic fistula rate compared with the nonstented group,[14] and it has been reported that patients with a soft pancreas had a relatively higher incidence of pancreatic fistula when using the internal drainage stent, compared with a nonstented group.[15] Our randomized controlled trial has clarified that there was no difference in the pancreatic fistula rate in soft pancreas between groups with internal and external drainage tubes. Therefore, one can conclude that the type of drainage stent has no impact on the incidence of postoperative complications including pancreatic fistula. However, internal drainage is thought to provide an easy postoperative management and develop a fast-track

Table 3 Pancreatic texture and pancreatic fistula

	External drainage (n = 50)	Internal drainage (n = 50)	*P* value
All pancreatic fistulas			
Hard pancreas	6/35 (17.1%)	3/28 (10.7%)	.68
Soft pancreas	4/15 (26.7%)	10/22 (45.5%)	.64
Grades B + C			
Hard pancreas	1/35 (2.9%)	0/28 (0%)	.99
Soft pancreas	2/15 (13.3%)	3/22 (13.6%)	.99

The incidence of pancreatic fistula showed no significant difference between the external drainage group and the internal drainage group.

Table 4 Postoperative status of remnant pancreas

	External drainage (n = 50)	Internal drainage (n = 50)	*P* value
Serum gastrin level, pg/mL*	62 (16–735)	60 (11–520)	NS
Output of pancreatic juice, mL*	75 (0–500)	ND	NS
Fasting blood sugar level, mg/dL†	98 (75–255)	101 (82–336)	NS
Serum hemoglobin A1c level, %†	5.3 (3.9–11.2)	5.4 (4.3–8.1)	NS
Body weight gain†,‡	.89 (.83–1.03)	.9 (.78–1.05)	NS
Severe diarrhea†,§	0	0	NS
Dilatation of remnant pancreatic duct‖	1	0	NS

Postoperative status of remnant pancreas showed no significant difference between the external drainage group and the internal drainage group. Values are given as median (range) or *n*.

ND = not detected; NS = not significant.

*Postoperative day 14.

†Postoperative month 6.

‡Preoperative body weight divided by postoperative body weight.

§Grades 3 or 4 according to the National Cancer Institute Common Toxicity Criteria, version 3.

‖Postoperative month 6 by computed tomography.

postoperative course. In the future, we mention to clarify the role of stent tube, compared with no stent, for pancreaticoduodenectomy.

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Original Article

Phase I/II study of a fine-powder formulation of cisplatin for transcatheter arterial chemoembolization in hepatocellular carcinoma

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Aim: The clinical feasibility of transcatheter arterial chemoembolization (TACE) with fine-powder cisplatin (CDDP) in patients with hepatocellular carcinoma (HCC) has not been investigated. A phase I/II study was conducted to investigate the safety and tolerability of fine-powder CDDP when it was used with lipiodol and gelatin sponge particles for TACE.

Methods: Fine-powder CDDP emulsified in lipiodol was injected into tumor arteries. Embolization was subsequently performed with gelatin sponge particles. The CDDP dose was started at 45 mg/m^2 (level 1) and increased to 65 mg/m^2 in 10 mg/m^2 increments.

Results: Thirteen patients were enrolled in phase I study since no dose limiting toxicity was observed in any patients, even in seven patients at level 3 (65 mg/m^2), the recommended dose was 65 mg/m^2. The major adverse event was grade 3 thrombocytopenia, which occurred in 8% of patients. The incidence of hematological toxicities was 15% for leukocytopenia, 84% for thrombocytopenia, and 84% for anemia. Increased serum total bilirubin was observed in 54% and increased aspartate aminotransferase or alanine aminotransferase in all patients. All digestive tract symptoms (nausea 77%, anorexia 84%, vomiting 31%) were grade 2 or lower. Total adverse events were grade 3 or higher in 44%. The response rate in 19 patients who received the recommended dose was 21%.

Conclusions: TACE with a fine-powder formulation of CDDP at a dose of 65 mg/m^2 is well tolerated in patients with unresectable HCC.

Key words: cisplatin, hepatocellular carcinoma, transcatheter arterial chemoembolization

INTRODUCTION

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE) is a widely used treatment for unresectable hepatocellular carcinoma (HCC).[1] Gelatin sponge particles are mainly used for embolization, and almost always in conjunction with lipiodol.[2] Doxorubicin (DXR), epirubicin (EPI), mitomycin C, cisplatin (CDDP), and others, have been used as anticancer agents, and response rates range from 15% to 73%.[3–8]

The response rate to TACE with CDDP varies (15–73%).[3,4,7] The standard concentration of CDDP solution in Japan (0.5 mg/mL) cannot be mixed with an appropriate dose of lipiodol. A fine-powder formulation of CDDP (IA-call®, Nippon Kayaku, Tokyo) has recently been developed, making possible the preparation of high-concentration aqueous solutions. The response rate was 33.8% against HCC by hepatic arterial infusion with high-concentration CDDP solutions (1.43 mg/mL). Moreover, unlike conventional preparations, fine-powder CDDP is readily miscible when mixed with lipiodol and thereby easy to use for TACE. However, the safety and tolerability of using fine-powder CDDP for TACE is unknown in patients with HCC.

We conducted a phase I/II study of fine-powder CDDP for TACE using lipiodol and gelatin sponge particles in HCC patients. The primary objectives of this study were to evaluate the safety and tolerability of fine-powder CDDP, and to determine the recommended dose (RD). The secondary objective was to evaluate the tumor response.

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PATIENTS AND METHODS

Patient eligibility

THE ELIGIBILITY CRITERIA for enrollment in this study were: (i) unresectable HCC confirmed histologically or clinically by diagnostic imaging; (ii) measurable lesions confined to the liver, and no thrombosis of the portal vein trunk; (iii) no prominent arteriovenous shunt or arterio-portal shunt; (iv) no lingering effect of previous therapy (at least a 6-week interval should follow the cessation of the other therapy); (v) Eastern Cooperative Oncology Group performance status score of 0 or 1; (vi) maintenance of adequate bone marrow, kidney, and cardiac function, and meeting the following clinical laboratory test criteria: leukocytes count, 3000/mm^3; platelet count, 50,000/mm^3; hemoglobin, 9.0 g/dL; serum creatinine, the upper limit of the normal range; BUN, 25 mg/dL; serum total bilirubin level, 2.0 mg/dL; (vii) age, ≥20 years but <80 years; (viii) Child–Pugh class A or B; (ix) life expectancy of at least 12 weeks; (x) written informed consent from the patient.

The exclusion criteria were clinically evident congestive heart failure, serious cardiac arrhythmia, active or symptomatic coronary artery disease or ischemia, active clinically serious infections, seizure disorder requiring medication, history of organ allograft, prior malignancy (any cancer curatively treated >3 years prior to entry was not an exclusion criterion), a history of serious hypersensitivity to drugs and contrast medium, and, in women, pregnancy or lactation. Patients that a physician judged to be inappropriate for other reasons were also excluded.

This protocol was approved by the Nihon University School of Medicine Institutional Review Board for Clinical Investigation, and the study was conducted in compliance with the provisions of the Declaration of Helsinki and local laws and regulations.

Treatment methods

The prepared emulsion (consisting of fine-powder CDDP, a small quantity of contrast medium, and lipiodol [Lipiodol Ultra-fluide®; Laboratoire Guerbet, Aulnay-sous-Bois]) was selectively injected through a microcatheter into the arteries supplying the tumor. It was possible to slow the rate of injection or to discontinue injection if retrograde flow occurred. Embolization was subsequently performed with gelatin sponge particles (Gelpart; Nipponkayaku). To prevent renal damage, adequate hydration was ensured before and after TACE administration by intravenous drip of 1000–2000 mL of an electrolyte infusion. Because of the potentially high incidence of nausea and vomiting, 10 mg of azasetron hydrochloride (5-HT_3 antagonist) and 8 mg of dexamethasone were administered to all patients prophylactically.

Study design

This study was a non-randomized, uncontrolled, non-blinded, single-hospital phase I/II study to investigate the tolerability and safety of fine-powder CDDP as used with lipiodol and gelatin sponge particles for TACE.

To determine the dose limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended dose (RD), fine-powder CDDP started at 45 mg/m^2 (level 1), 55 mg/m^2 (level 2) and 65 mg/m^2 (level 3) followed by dose escalation. Three patients were treated at a particular dose level. If none of the 3 patients experienced DLT, the subsequent cohort was treated at the next higher dose level. If 1 of 3 patients experienced DLT at a dose level, additional 3 patients were entered at that dose level. Then, if one of six patients experienced DLT at this dose level, the subsequent cohort was treated at the next higher dose level. If more than one of three or more than two of six patients experienced DLT, the subsequent cohort was treated at the next lower dose level. MTD was defined as the dose level that produced DLT in two of six patients or that level immediately below the one that produced DLT in more than two of 6 or more than one of three patients.

DLT was defined as: (i) grade 3 or grade 4 non-hematological toxicity; (ii) grade 4 leukocytopenia or neutropenia for 14 days; (iii) grade 4 thrombocytopenia for 14 days; (iv) grade 4 elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) for 7 days; (v) grade 3 hyperbilirubinemia for 14 days; (vi) grade 3 elevation of serum creatinine for 7 days; (vii) grade 3 neutropenia with fever of ≥38.5°C; (viii) liver abscess, cholangitis, and cholecystitis requiring interventional radiology, endoscopic treatment or surgical care. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0. We set the upper dose limit at 65 mg/m^2, and did not reduce dose of CDDP by tumor size.

This upper limit was based on the results of a preliminary dose-finding study in which 25–80 mg/m^2 was administered intra-arterially to 12 HCC patients (MTD, 80 mg/m^2; RD, 65 mg/m^2).[9] We thought that severe adverse events were caused by embolization. Therefore, we decided to use the RD as the upper limit in hepatic arterial infusion. The phase II study was conducted at this RD in 19 patients with HCC.

Pharmacokinetics

Blood samples for the determination of plasma concentrations of platinum (total and free) were collected prior to TACE and hepatic arterial infusion (HAI), as well as immediately, 0.5, 2, 6, 24 and 96 h after TACE and HAI. Total platinum was analyzed by using an aliquot of unfiltered plasma. Free platinum was analyzed by using an Amicon Centrifree® micropartition system (Millipore, Billerica, MA). Samples were stored at −20 °C until analyzed.

Clinical assessment

A physical examination, complete blood cell counts, and serum chemistries were carried out at baseline and at least one month after TACE. Contrast-enhanced computed tomography (CT) was performed to evaluate the tumor at the time of pretreatment and one month after TACE. The antitumor effect was evaluated by using the response evaluation criteria in solid tumors (RECIST) guidelines.[10] Therefore, we do not consider it about deposit in the tumor of lipiodol and tumor necrosis. Anti-tumor effect was evaluated after first-time TACE.

RESULTS

Patient characteristics

THE PHASE I/II study was conducted in 25 patients between March 1 and May 31, 2008. Their characteristics are shown in Table 1. Only 1 patient had Child-Pugh B cirrhosis. Median tumor size was 20 mm (range: 10–180 mm). Eight patients had single tumors and 17 had multiple tumors. Fourteen cases were positive for hepatitis C virus (HCV), five were positive for hepatitis B virus (HBV), and six were negative for both. Prior treatments included resection in 11 patients, TACE in seven patients, a combination of resection and TACE in three patients, and no treatment in four patients.

Toxicity

As for the appearance of DLT, no patient was recognized in level 1 (45 mg/m^2), level 2 (55 mg/m^2). Since DLT did not develop before treatment was completed in the 3 patients at dose level 3 (65 mg/m^2), we added four patients to confirm RD. DLT was not observed at this dose. Therefore, the phase I study was completed with a total of 13 patients. The adverse events in the phase I study are shown in Table 2. The RD was determined to be 65 mg/m^2. Since 65 mg/m^2 had been established as the upper limit in this study, it was impossible to determine the MTD and DLT.

Table 1 Patient characteristics in phase I/II study (n = 25)

Sex	
Male	21
Female	4
Age (year)†	68 (45–79)
PS 0	25
Child–Pugh classification	
A	24
B	1
Viral marker	
HBV+ HCV−	5
HBV− HCV+	14
HBV− HCV−	6
Previous treatment	
Resection	11
TACE	7
Resection+TACE	3
Non	4
Vascular invasion	
Absent	18
Present	7
Tumor number	
Single	8
Multiple	17
Maxmum tumor size (mm)†	20 (10–180)
Tumor stage‡	
I	5
II	13
IIIA	7

†Median (range); ‡UICC TNM classification. HBV, hepatitis B virus; HCV, hepatitis C virus; PS, Eastern Cooperative Oncology Group performance status; TACE, transcatheter arterial chemoembolization.

After determination of the RD, 12 patients were added, and a phase II study was conducted. Adverse events by dose level are shown for all patients in Table 3. At the RD (level 3), leukocytopenia occurred in one patient (5%), anemia in 10 patients (53%), thrombocytopenia in 17 patients (89%), total bilirubin (TB) elevation in nine patients (47%), AST/ALT elevation in 19 patients (100%), creatinine elevation in one patient (5%), vomiting in 12 patients (63%), nausea in 16 patients (84%), and anorexia in 17 patients (89%). Grade 3 and 4 adverse events were thrombocytopenia in one patient (5%) and AST elevation and ALT elevation in eight patients (42%) and nine patients (47%), respectively. Grade 3 or higher non-hematological toxicity (AST/ALT elevation) occurred in 11 of 25 patients (44%) and Grade 3 or higher hematological toxicity (thrombocytopenia) occurred in two patients (8%). Grade 4 toxicity (AST/ALT elevation) occurred in only one patient.

Table 2 Adverse events in phase I study ($n = 13$)

Grade	1	2	3	4	All grade (%)	Grade 3/4 (%)
Hematological						
Leukocytopenia	1	1	0	0	2 (15%)	0
Anemia	6	5	0	0	11 (84%)	0
Thrombocytopenia	5	5	1	0	11 (84%)	1 (8%)
Non-hematological						
Anorexia	5	6	0	0	11 (84%)	0
Nausea	4	6	0	0	10 (77%)	0
Vomiting	3	1	0	0	4 (31%)	0
Elevated total bilirubin	2	5	0	0	7 (54%)	0
Elevated AST	1	7	5	0	13 (100%)	5 (38%)
Elevated ALT	3	6	4	0	13 (100%)	4 (31%)
Elevated creatinine	0	0	0	0	0	0
Renal failure	0	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The course of adverse events after TACE is shown in Table 4. The peak AST/ALT elevation most commonly occurred on day 2, and grade 3 or 4 AST elevation and ALT elevation were observed 1 week after TACE in 1 case (4%) each. Thrombocytopenia developed on day 3–5, and even though the rate was high (84%) 1 week later, it fell to 20% 1 month later.

Pharmacokinetics

Plasma concentration-time curves for intra-arterial infusion of CDDP at 65 mg/m^2 that are the RD in HAI without and with lipiodol are shown (Fig. 1). In all points, sample with lipiodol (TACE) is less than the total platinum concentration in comparison with sample without lipiodol (HAI). Free platinum concentration became under the limits of measurement at 6 h after infusion both. However, at 2 h after infusion, free platinum concentration with lipiodol (TACE) was higher than without lipiodol (HAI) (Fig. 2).

Response

According to RECIST criteria, CR did not occurred in any of the 25 patients, PR in six patients, SD in 18 patients, and PD in one patient; the response rate was 24%. With

Table 3 Adverse events according to dose level in all patients

	All grades			Grade 3/4		
	Level 1–2 ($n = 6$)	Level 3 ($n = 19$)	Total ($n = 25$)	Level 1–2 ($n = 6$)	Level 3 ($n = 19$)	Total ($n = 25$)
Hematological						
Leukocytopenia	1 (17%)	1 (5%)	2 (8%)	0	0	0
Anemia	5 (83%)	10 (53%)	15 (60%)	0	0	0
Thrombocytopenia	4 (67%)	17 (89%)	21 (84%)	1 (17%)	1 (5%)	2 (8%)
Non-hematological						
Anorexia	4 (67%)	17 (89%)	21 (84%)	0	0	0
Nausea	4 (67%)	16 (84%)	20 (80%)	0	0	0
Vomiting	1 (17%)	12 (63%)	13 (52%)	0	0	0
Elevated total bilirubin	3 (50%)	9 (47%)	12 (48%)	0	0	0
Elevated AST	6 (100%)	19 (100%)	25 (100%)	3 (50%)	8 (42%)	11 (44%)
Elevated ALT	6 (100%)	19 (100%)	25 (100%)	2 (33%)	9 (47%)	11 (44%)
Elevated creatinine	0	1 (5%)	1 (4%)	0	0	0
Renal failure	0	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4 Recovery from adverse events of all patients

Time after TACE	All grades		Grade 3/4	
	7 days	30 days	7 days	30 days
Hematological				
Leukocytopenia	2 (8%)	3 (12%)	0	0
Anemia	8 (32%)	3 (12%)	0	0
Thrombocytopenia	21 (84%)	5 (20%)	0	0
Non-hematological				
Anorexia	6 (24%)	2 (8%)	0	0
Nausea	0	0	0	0
Vomiting	0	0	0	0
Elevated total bilirubin	3 (12%)	4 (16%)	0	0
Elevated AST	20 (80%)	5 (20%)	1 (4%)	0
Elevated ALT	22 (88%)	3 (12%)	1 (4%)	0
Elevated creatinine	0	1 (4%)	0	0
Renal failure	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization.

respect to the RD patients ($n = 19$), CR did not occurred in any patients, PR in four patients, SD in 14 patients, and PD in one patient; the response rate was 21% (Table 5). If we regarded lipiodol accumulation lesions in tumors as being not viable or necrosis, and theses lesions were excluded from the tumor size, response rate was 76% (CR,10; PR,9; SD,5; PD,1).

In total, TACE using CDDP was enforced 67 times in 25 patients during this study. Serious adverse events were not common and suggest that TACE using CDDP is safe.

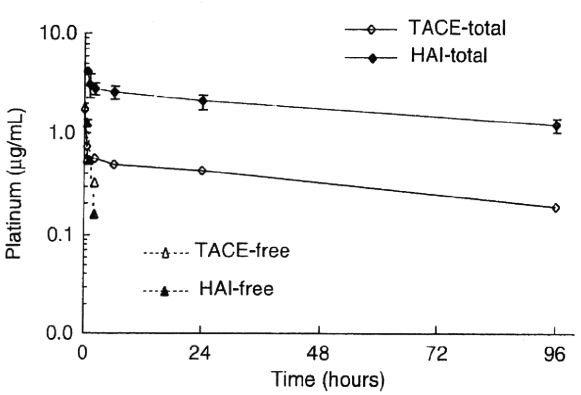

Figure 1 The concentration-time curves of total and free platinum in plasma. Cisplatin dose were 65 mg/m^2 both transcatheter arterial chemoembolization (TACE) with lipiodol, and hepatic arterial infusion (HAI) without lipiodol.

DISCUSSION

THIS PHASE I/II study demonstrated that fine-powder CDDP had a favorable safety and tolerability profile for patients with unresectable HCC who are treated with TACE. The dose 65 mg/m^2 can be recommended for future studies in Japanese patients with HCC. The response rate was 21%. There are no reports of the evaluation in RECIST in TACE using DXR or EPI. Therefore a phase II/III study with TACE using DXR or EPI for will be necessary.

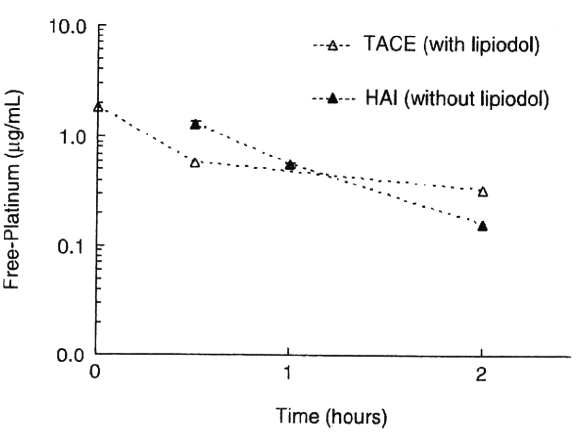

Figure 2 The concentration-time curves of free platinum in plasma. At 2 h after infusion, free platinum concentration with lipiodol (transcatheter arterial chemoembolization; TACE) was higher than without lipiodol (hepatic arterial infusion; HAI).

Table 5 Tumor response

	CR	PR	SD	PD	Response rate
All patients ($n = 25$)	0	6	18	1	24%
RD cases ($n = 19$)	0	4	14	1	21%

CR, complete response; PD, progressive disease; PR, partial response; RD, recommended dose; SD, stable disease.

CDDP is mainly excreted by kidneys, and its DLTs are nephrotoxicity, neurotoxicity, and hematologic toxicity.[11] Yoshikawa *et al.*[9] observed non-hematological toxicities (anorexia, vomiting, fever, general fatigue) in more than 30% of patients intra-arterially injected with fine-powder CDDP, and severe adverse events (grade 3 or higher) including anorexia (22.5%), vomiting (6.3%), and abdominal pain (1.3%). In addition, they reported grade 3 or higher thrombocytopenia (25.0%), neutropenia (13.0%), anemia (1.3%), AST/ALT elevation (11.3%), TB elevation (3.8%), and creatinine elevation (32.5%/2.5%). In this study, only grade 2 anorexia in four cases (21%) and vomiting in six cases (32%) were observed at the 65 mg/m^2 dose. In the present study, the incidence of grade 3 or more adverse events (expressed as % of all cases) was AST/ALT elevation (44) and thrombocytopenia (8) (Table 3). The reason for the lower rates of anemia, TB elevation, and creatinine elevation in their report appears to have been differences in the background characteristics of the eligible patients, and probably the differences in the plasma concentration platinum. On the other hand, the greater effect of embolization may account for the high rate of AST/ALT elevation.

The incidences of vomiting, thrombocytopenia, and anorexia tended to be higher at dose level 3 than at level 1–2. More specifically, vomiting was 17% at level 1–2, but increased to 63% at level 3. Thrombocytopenia and anorexia increased from 67% to 89%, respectively. Thus, caution should be exercised when the dose of CDDP is escalated (Table 3).

A separate phase I/II clinical study of TACE with a mixture of fine-powder CDDP and lipiodol was carried out by Yamashita *et al.* They reported an RD of 35 mg/m^2, and vomiting as the DLT.[12] In our study, the RD was 65 mg/m^2 even though TACE was performed using gelatin sponge particles and lipiodol. We think that the 5-HT$_3$ antagonist and steroid (administered by intravenous drip to every patient before TACE in our study) lowered the incidence of grade 3 vomiting.

The rate of response to fine-powder CDDP plus lipiodol (for all cases, 24%) was worse than the rate of response to fine-powder CDDP alone.[9] That is thought to be because lipiodol accumulates in and around the tumors and makes it difficult to accurately detect changes in tumor size on CT, and because all of the imaging evaluations were performed after one TACE session. Long-term follow-up of the efficacy of TACE with fine-powder CDDP seems to be necessary.

CDDP activity is concentration-dependent and time-dependent. Court *et al.* showed that the first-pass uptake of CDDP by tumors following intra-arterial delivery of 50 mg/m^2 at a rate of 1 mg/min to six HCC patients was 48.8% (range, 34.2–55%).[13] Therefore, CDDP should accumulate in liver tumors at even higher concentrations and have more therapeutic efficacy if CDDP is mixed with lipiodol and if injection is via the hepatic artery, both of which facilitate CDDP retention by the tumor.

In conclusion, TACE using gelatin sponge particles and lipiodol mixed with fine-powder CDDP at a dose of 65 mg/m^2 is well tolerated in patients with unresectable HCC.

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REVIEW

The technical advance and impact of caudate lobe venous reconstruction in left liver: additional safety for living-related donor liver transplantation

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caudate lobe, hepatic vein reconstruction, living-related donor liver transplantation.

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Summary

The key to obtaining good overall outcomes in small-for-size liver-graft transplantation is ensuring sufficient blood flow to the graft during the initial period after surgery. In left lobe liver grafting, various reconstruction techniques have been devised to maximize the limited graft volume. The reconstructions of the caudate lobe (CL) vessels were one of the main streams. In this article, we focus on the clinical significance of CL vessel reconstructions after small-for-size liver-graft transplantation and discuss the roles of various techniques. These techniques contribute to the enlargement of the margin of safety with respect to small-for-size liver-graft transplantation.

Introduction

Advances in surgical procedures and perioperative management have extended the application of small-for-size liver-graft transplantation. As a result, the number of small-sized liver grafts has been increasing. The criterion for the minimum graft size to adults has been defined as more than one-third in the ratio of the predicted graft volume/standard liver volume of the recipient. The graft volume and function together is an independent predictor of mortality during the early postoperative period [1]. While addressing this issue, performance of the concomitant caudate lobe (CL) resection has been a standard procedure for donor hepatectomy in marginal size graft. Left liver plus CL graft is a useful option for adult living-related donor liver transplantation (LDLT), because the addition of the CL can provide an 8–12% increase in graft weight [2].

Serious problems can affect grafts, especially in the initial few weeks after small-for-size liver-graft transplantation. Blood-vessel deformation and stenosis caused by rapid graft regeneration can be lethal [3]. One of the major challenges in LDLT is small vessels reconstruction in small-for-size liver grafts. Various reconstruction techniques have been devised to minimize vessel deformation and increase blood flow to the CL, to ensure full functioning of the graft. These techniques might increase the margin of safety for small-for-size liver-graft transplantation.

In this article, we summarized the advances made in the techniques and impact of CL venous reconstruction in left liver graft for increasing additional safety margin in living-donor-related liver transplantation.

Outflow reconstruction

Classical end-to-side direct anastomosis of a liver graft to the inferior vena cava (IVC) can cause twisting and deformation at the anastomotic site because of graft regeneration. This is significant in the first few weeks after surgery, when the caval window of the IVC is thin and the distance from the IVC is short [3]. End-to-end

anastomosis has been widely used to overcome this problem. A large orifice with two (left and middle hepatic veins) or three (left, middle, and right hepatic veins) major hepatic veins is commonly created at the recipient site [2]. Various reconstruction techniques (simple venoplasty, septoplasty, rectangular plasty, venoplasty with a vein graft patch, and creation of a wide circular cuff by vein grafting) are used depending on the grafted vessels [4–7].

In recent cases with a marginal predicted graft size relative to the recipient's metabolic demand, the short hepatic vein (SHV) was aggressively reconstructed [3,8]. Venous drainage from the CL occurred through the SHV and intraparenchymal communication. Good blood flow from other segments to the CL parenchyma might have facilitated graft growth. Without SHV reconstruction, the CL was often atrophied or regenerated slowly [9].

As reported in a previous study, the regeneration rates of the CL and other segments 1 month after LDLT without SHV reconstruction were 62 ± 24% and 152 ± 35%, respectively [10]. This was potentially attributable to insufficient venous drainage from the CL. By contrast, the regeneration rate of the CL with SHV reconstruction was greater than or equal to those of other segments. When the SHV was <3 mm in diameter or near the main hepatic vein, it had poor significance for reconstruction and the drainage domain was small. Caudate lobe regeneration was dependent on the tissue-perfusion area. In one study, a single SHV suitable for reconstruction was found in 22 out of 27 (81.5%) donors. The CL blood flow was classified according to the perfusion state as good (n = 15; 142.6 + 31.4%), fair (n = 7; 118.4 + 22.4%) or poor (n = 5; 90.1 + 36.5%) [9].

As shown in Fig. 1, the one-orifice technique simultaneously allows complete drainage of all veins, including the SHV, and minimal deformation of the outflow channel [7,11]. It can be used when there is a long distance between the IVC and SHV. The advantage of this method

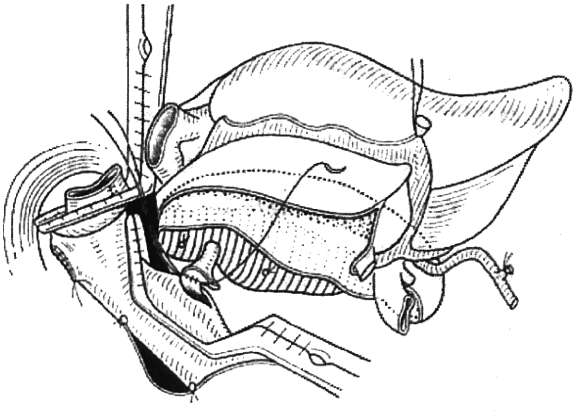

Figure 2 The conventional end-to-side direct anastomosis of the short hepatic vein to the inferior vena cava (IVC). Double outflow reconstructions were performed. (Main hepatic veins and short hepatic vein.) (Takayama *et al. J Am Coll Surg* 2000).

is that there were adequate suture margins between the IVC and the liver graft and single *in situ* vessel anastomosis. All intricate surgical procedures are performed on the back table, and a wide venous reservoir of the liver graft is simply attached end-to-end to the caval window. The vein graft functions as a circular cuff and conduit from the SHV. While it appears that the regeneration rate of the CL tends to be higher than that after conventional end-to-side SHV reconstructions (Fig. 2), this proposition needs further confirmation in more trials.

Inflow reconstruction

The isolated portal branch of CL is generally thin and not conventionally used in adult LDLT. An isolated portal branch of CL was found in 13.4% (9/67) of the donors, and 4.5% (3/67) of the cases were suitable for reconstruction [12].

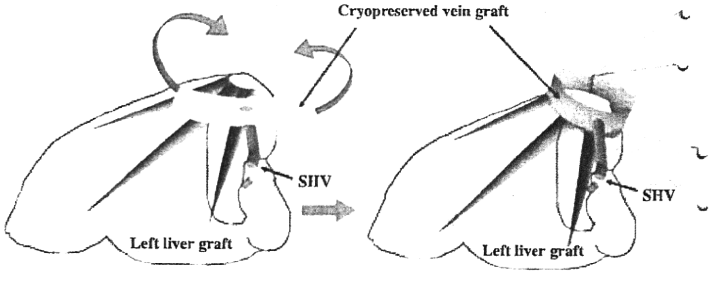

Figure 1 The one-orifice technique of the left liver graft. It allows complete drainage of all veins, including the SHV, and minimal deformation of the outflow channel. It can be used when there is a long distance between the inferior vena cava (IVC) and SHV. (Yamazaki *et al. Liver Transpl* 2009.)

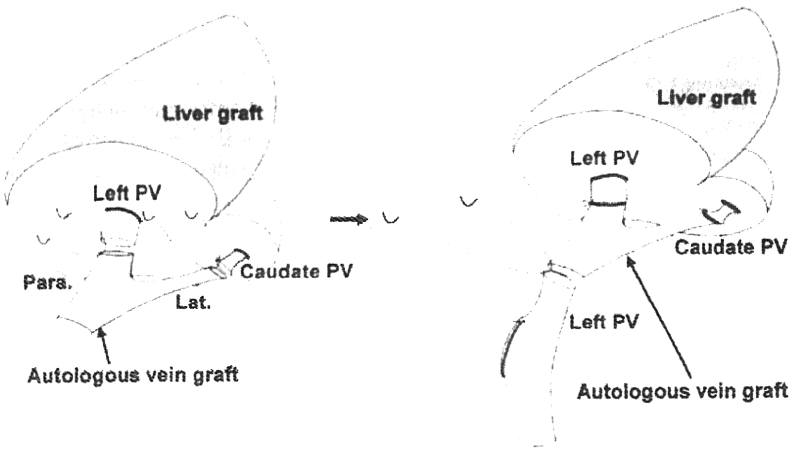

Figure 3 The autologous interposition methods of the portal vein (PV) reconstruction. The PV graft was extracted from the recipient's right PV branch together with the paramedian and lateral branches. The extracted autologous vein graft was interposed to the recipient's left PV branch in the back table. The lateral branch was sutured to the caudate PV and the paramedian branch was sutured to the left PV of the liver graft. (Yamazaki *et al. Liver Transpl* 2005.)

As reported in previous studies, an isolated portal branch of CL with a diameter <2 mm was considered to have poor significance for reconstruction, whereas CL inflow reconstruction was aggressively performed after small-for-size liver-graft transplantation when the diameter was >2 mm. The portal branch of CL was selected depending on the diameter and proximity to the left portal vein (PV) during graft harvesting. It was preserved with part of the recipient's PV like the Carrel's cuff. The recipient's autologous vein graft of the left PV with isolated portal branch of segment 1 or the right PV branches were used in most case (Fig. 3). The extracted PV together with the branches was interposed and extended [12,13]. Hence, inflow reconstruction may have a potential impact on small-for-size liver-graft transplantation.

Discussion

The graft-size mismatching is the most critical factor for success in LDLT while technical advances have enabled the use of relatively small-for-size grafts. The graft blood flow in the initial few weeks after surgery was reported to influence the overall outcome of small-for-size liver-graft transplantation [1]. Small-for-size grafts can experience problems relating to high PV pressure and high growth demands. Persistent PV hypertension and overperfusion in the initial few days after LDLT is the trigger of small-for-size syndrome (SFSS). Graft to recipient weight ratio of <1.0%, or <30% to 50% of standard/estimated liver volumes, have been used to define SFSS in previous studies [14,15]. The clinical manifestations of SFSS include delayed synthetic function followed by prolonged parenchymal damage of the liver. It also leads to prolonged cholestasis, coagulopathy, gastrointestinal bleeding, hyperbilirubinemia, and nonfunction or loss of the primary graft [16]. The pathogenesis of the SFSS is periportal injury in most cases. Whether the additional impact of the CL transplantation and revascularization contributes to the graft pressure gradients is unknown.

Although the CL volume is small, it is important when the graft volume is critical. Ikegami *et al.* have shown that the regeneration rate of the transplanted CL and other left lobe graft segments. The regeneration rate of the CL 1 month after transplantation was smaller (62 ± 24%) than that of other left lobe graft segments (152 ± 35%). With reconstruction of the inflow [12] or outflow [7], the regeneration rate of the CL was noted to be equal to or more than that of the other left lobe graft segments. The additional functional volume afforded by CL venous reconstruction might provide an additional safety margin.

As shown in Table. 1 various CL venous reconstruction techniques were devised as one of the feasible solutions to overcome the small-for-size graft. The CL outflow reconstruction is now widely performed and suitable for most left liver grafts. Direct anastomosis of the hepatic veins to a thin IVC can sometimes cause a bend at the anastomotic site, which results in outflow occlusion. The deformation of the outflow anastomosis caused by graft regeneration can lead to hepatic vein stenosis and graft congestion. This phenomenon is common when the outflow tract is narrow and the distance from the IVC is short. To overcome these problems, techniques for reconstructing hepatic vessels have been reported [8]. The CL regeneration rate might depend on the blood drainage to the reconstructed SHV. The width and length of the SHV are indicators of the adequacy of the blood flow. When

Table 1. The trends in the left liver plus caudate lobe venous reconstruction.

Author	Year	Reconstruction	Procedure
Miyagawa	1998	Without reconstruction	
Takayama	2000	Outflow	End-to-side
Ikegami	2001	Without reconstruction	
Sugawara	2002	Outflow	End-to-end
Kokudo	2004	Inflow	Autologous vein graft: recipient's left portal branch
Hwang	2004	Outflow	ND
Hashimoto	2005	Outflow	Cryopreserved vein graft wrapping
Yamazaki	2005	Inflow	Autologous vein graft: recipient's right portal branch

ND, not discussed.

the graft size is marginal with respect to the recipient's metabolic demand, outflow reconstruction of the SHV might have particular value. According to Couinaud's study, 69% (66/96) of CLs have a single vein and most of all the veins directly entered to the vena cava [17]. This result shows that the largest SHV reconstruction is the optimal method for outflow reconstruction.

To assure full graft viability and functioning, all of the feeding and drainage vessels for the CL should be reconstructed. However, it would be difficult to add inflow reconstruction of the portal branch of CL to the standard operation schedule, because it is possible in only <5% of all reported cases [12]. Inflow vascular reconstruction reportedly facilitates graft growth and small-for-size liver-graft transplantation; however, the operation time and liver-graft cold-preservation time on the back table are longer than those for procedures without revascularization. Recently, Kokudo *et al.* reported that the existence of isolated caudate PV was encountered in only 5.9% of 67 donors. Thereafter, only one case was reported about CL inflow reconstruction [13]. Thus, more results are needed to estimate the clinical value of caudate lobe PV reconstruction.

Inflow reconstruction thus is only of theoretical interest at present.

Complex venous reconstruction requires autologous and/or cryopreserved vein grafts, the use of which remains controversial. The main issues associated with cryopreserved vein grafts are the prolonged cold-ischemic time, underlying diseases, and graft shortages. The cryopreserved vein graft contains high rates of complications, such as aneurysm, thrombosis, and stricture of cryopreserved vascular grafts. Kuang *et al.* [18] report that six out of the seven vein grafts were complicated in a study published in 1996. Millis *et al.* [19] followed the report in pediatric patients, wherein 22 out of 42 patients (52%) encountered vein graft stenosis and thrombus. Recently, Sugawara *et al.* [20] reported that the preservation of integrity of patency of the cryopreserved vein graft used in transplant in 5 years was 58%. The complication rate of the cryopreserved vein graft is higher than that of autologous vein graft. Thus, the use of cryopreserved vein graft should be limited when autologous vein graft are available. Evidence of the larger outcomes is lacking and long-term follow-up remains necessary in this category of transplant recipients.

In conclusion, there is significant impact of the CL venous reconstruction in left liver graft. During liver harvesting, particular effort should be made to preserve the caudate branches in case of small-for-size liver grafting.

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Recent Advances in Chemotherapy for Advanced Gastric Cancer in Japan

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Abstract
In the early 1990s, a combination of 5-fluorouracil (5-FU) and cisplatin was widely adopted to treat advanced gastric cancer; however, no survival advantage over single-agent 5-FU was confirmed by the results of randomized trials conducted over a long period. Recently developed agents such as irinotecan, taxanes (docetaxel), and new oral fluorouracil (S-1) have yielded more promising results, with a response rate of over 50% and a median survival time of over 10 months in combination studies. These newer combination regimens were investigated in various randomized phase III studies to clarify if the newer-generation regimens provided a survival advantage over the older-generation regimens. Based on the findings of a large randomized study, S-1 has become standard in the adjuvant setting after D2 dissection curatively resected stage II and III gastric cancer. This article reviews the recent advances in gastric cancer chemotherapy, especially in Japan.

Key words Gastric cancer · Chemotherapy · Standard chemotherapy

Introduction

Gastric cancer (GC) is the most common malignancy in Japan. In 1998, more than 100000 new cases were reported[1] and by 2015, it is anticipated that this number will have climbed to nearly 150000.[2] The only potentially curative treatment for GC is surgical resection of all of the gross and microscopic disease; however, recurrence is common, both in regional and distant sites. The standard treatment for advanced or relapsed gastric cancer (AGC) is chemotherapy, aimed at prolonging survival.

Until about 10 years ago, there were few medical oncologists in Japan, and gastrointestinal surgeons played the part of oncologists in designing cancer chemotherapy for patients with gastric or colorectal carcinomas. The educational systems for medical oncologists were initiated by the Japan Society of Medical Oncology (JSMO). However, from 2005 to 2007 only 205 specialists in medical oncology passed the JSMO examination. The JSMO predicts that 80 medical oncologists will be initiated into the system each year, but this will be insufficient to cover all patients who have AGC. Thus, surgeons must continue to treat their patients with AGC oncologically in Japan. Our aim in writing this review is to make surgeons aware of the widely used regimen or standard chemotherapy for GCs, because we expect them to be able to treat their AGC patients effectively and safely.

Anticancer Drugs for AGC

One of the most widely studied single-agent chemotherapies is the antimetabolite, 5-fluorouracil (5-FU), which confers response rates of approximately 20%.[3,4] Tumor antibiotics (mitomycin C, doxorubicin, and epirubicin), heavy metals (cisplatin and carboplatin), taxanes (paclitaxel and docetaxel), and camptothecins (irinotecan and topotecan) have also been evaluated in the treatment of AGC and afford response rates ranging from 5% to 30%.[5–7] Newer fluorinated pyrimidines such as the 5-FU prodrug, UFT (uracil and tegafur), and 5-FU derivatives such as S-1, are of particular interest since they can be administered orally and allow for mimicking of conventional infusional therapy.

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Is Chemotherapy Effective Against AGC?

Several combination chemotherapeutic regimens have been evaluated for their efficacy and tolerability in the treatment of AGC. They often achieve adequate response rates with variable toxicity in previously untreated AGC patients. Compared with the best supportive care, the median survival with combination chemotherapy appears to be increased by 2 months or longer.[8,9]

Standard Chemotherapy for AGC in Western Countries

In Western countries, FAM (5-FU/adriamycin/mitomycin C), FAMTX (5-FU/adriamycin/methotrexate), ELF (etoposide/leucovorin/5-FU), and CF (cisplatin/5-FU) regimens have been compared in several studies. In consideration of their moderate activity, we do not recommend that any of the evaluated regimens be regarded as the standard treatment. In a prospective, randomized phase III study, Waters et al.[10] compared a combination of epirubicin, cisplatin, and 5-FU (ECF) with FAMTX in previously untreated patients with AGC. This ECF regimen resulted in significantly higher response rates (46% vs 21%), median survival (8.7 vs 6.1 months), and 2-year survival rates (14% vs 5%), and is the de facto standard treatment for AGC in Europe.

In a randomized phase III study (TAX325), Moiseyenko et al.[11] compared the efficacy and safety of cisplatin and 5-FU (CF) vs docetaxel, cisplatin, and 5-FU (TCF) as front-line therapy in patients with metastatic or nonresectable AGC. The final analysis revealed that the addition of docetaxel to CF resulted in significantly higher response rates (37% vs 25%, for TCF and CF, respectively). Time-to-progression, the primary study endpoint, was significantly higher in the TCF-treated patients than in the CF-treated patients (5.6 months vs 3.7 months, respectively; $P < 0.0004$). At the time of this interim analysis, the observed difference in median overall survival favored TCF over CF (9.2 vs 8.6 months, respectively; $P = 0.0201$). The common severe toxicities associated with TCF and CF included stomatitis (20.8% and 27.2% of subjects, respectively), lethargy (21.3% and 17.9%), diarrhea (20.4% and 8.0%), nausea (15.8% and 18.8%), vomiting (14.9% and 18.8%), and febrile neutropenia or neutropenic infection (30% and 13.5%). Based on the results of the TAX325 trial, TCF is regarded as standard chemotherapy in the United States.

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Until the early 1990s there was no standard chemotherapy in Japan, although 5-FU infusion, CF, and uracil-tegafur, and mitomycin C (UFTM) regimens were widely employed in the clinical setting. In a three-arm, large randomized phase III trial, Ohtsu et al.[12] compared 5-FU with CF and with UFTM. They found 5-FU to be equal to or better than UFTM in terms of response and survival. Although CF achieved a better response rate and progression-free survival (PFS) than 5-FU monotherapy, there was no difference in overall survival between these two arms (7.3 and 7.1 months for CF and 5-FU, respectively). 5-FU monotherapy remained as a reference arm in the next phase III trial of the JCOG group.

New Anticancer Agents

S-1 consists of a 1:0.4:1 molar ratio mixture of tegafur and two 5-FU-modulating substances: gimeracil (5-chloro-2,4-dihydroxypyrimidine, CDHP) and oteracil (potassium oxonate). Sakata et al.[13] investigated the efficacy of S-1 as a single chemotherapeutic agent in AGC patients in a late phase II study. Four cycles of S-1 were administered twice a day to 51 patients at a dose of 80 mg/m^2 per day. One complete response (CR) and 24 partial responses (PRs) were observed, with an overall response rate of 49%. The median survival time (MST) achieved by S-1 in a phase II study was 8 months and it was generally well tolerated, the major toxicities including anemia, leukopenia, granulocytopenia, diarrhea, malaise, and proteinuria.

Boku et al.[14] reported a phase II trial of cisplatin/CPT-11 combination chemotherapy involving 44 patients with AGC by the JCOG. Cisplatin was administered at a dose of 80 mg/m^2 on day 1, and CPT-11 was administered at a dose of 70 mg/m^2 on days 1 and 15 every 4 weeks. They reported 1 CR and 20 PR, with an overall response rate of 48.0%, and an MST of 9 months. The grade 4 major toxicities with this combination were leukopenia (9.0%), neutropenia (57.0%), thrombocytopenia (2.0%), and anemia (5.0%).

JCOG 9912 Trial

The JCOG conducted another three-arm, randomized phase III trial in 1999 (the JCOG 9912 trial), evaluating the superiority of cisplatin/CPT-11 over the reference arm 5-FU, and the noninferiority of S-1 to 5-FU. The MSTs achieved by 5-FU, cisplatin/CPT-11, and S-1 were 10.8 months, 12.3 months, and 11.4 months,