Table 4. CTC grade 3/4 AEs (>5% frequency in any arm)

AE, *n* (%)	Cediranib 20 mg + mFOLFOX6 ($n = 58$)	Cediranib 30 mg + mFOLFOX6 ($n = 56$)	Placebo + mFOLFOX6 ($n = 58$)
Decreased appetite	11 (19.0)	10 (17.9)	1 (1.7)
PPES	8 (13.8)	12 (21.4)	0
Diarrhoea	6 (10.3)	12 (21.4)	1 (1.7)
Hypertension	4 (6.9)	6 (10.7)	1 (1.7)
Peripheral neuropathy	5 (8.6)	3 (5.4)	2 (3.4)
Peripheral sensory neuropathy	2 (3.4)	5 (8.9)	2 (3.4)
Neutropenia	3 (5.2)	0	0
Ileus	0	0	3 (5.2)

AE, adverse event; CTC, Common Terminology Criteria; mFOLFOX6, modified FOLFOX6; PPES, palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome).

appetite, diarrhoea and pneumonia (all $n = 2$) were reported in multiple patients.

The incidence of grade 3/4 AEs was 66%, 75% and 36% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The most common grade 3/4 AEs are summarised in Table 4. The incidence of serious adverse events (SAEs) was 39.7%, 39.3% and 19.0% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. No AEs had an outcome of death.

Clinical laboratory evaluation showed that treatment with cediranib plus mFOLFOX6 caused decreases in leucocyte, neutrophil and platelet counts and an increase in thyroid-stimulating hormone, but no new clinically important trends were observed in either cediranib group.

The median duration of exposure was 241.5, 213.0 and 223.5 days in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The proportion of patients experiencing a dose reduction/pause was highest in the cediranib 30 mg group (83.9%) versus the cediranib 20 mg (79.3%) and placebo (56.9%) groups (supplemental Figure S2, available at *Annals of Oncology* online). The dose intensity of cediranib/placebo was lower in the 30 mg group compared with the 20 mg and placebo groups; the mean daily dose of cediranib was 16.6 and 22.8 mg in the cediranib 20 and 30 mg groups, respectively. Exposure to mFOLFOX6 was similar in all arms; the median numbers of cycles of 5-FU, leucovorin and oxaliplatin were 17.0, 17.0 and 12.5, respectively, in the cediranib 20 mg group, 14.0, 14.0 and 11.0, respectively, in the cediranib 30 mg group and 15.0, 15.0 and 11.5, respectively, in the placebo group. However, more patients in the cediranib 30 mg group (33%) stopped oxaliplatin >12 weeks before progression compared with those in the cediranib 20 mg (14%) or placebo (8%) groups.

soluble biomarkers

Median VEGF levels ranged from 47 to 55 pg/ml at baseline; during treatment, levels remained similar to baseline in the placebo group but increased in cediranib-treated patients. In the cediranib 20 mg group, levels increased to 89 pg/ml by day 28 and to ~130 pg/ml thereafter. In the cediranib 30 mg group, levels increased to 160–170 pg/ml from days 28 to 84 before decreasing to 151 pg/ml by day 112.

Median sVEGFR-2 levels ranged from 9095 to 10 126 pg/ml at baseline. In the placebo group, median levels decreased to 7204 pg/ml on day 112. In the cediranib 20 mg group, median levels decreased to 7091 pg/ml on day 28 and 6403 pg/ml on day 112. The corresponding median levels in the cediranib 30 mg group were 5836 and 5789 pg/ml.

extended follow-up

At second data cut-off, PFS events had been observed in 47 (81%), 46 (82%) and 46 (79%) patients in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The PFS HR for the cediranib 20 mg group versus placebo was 0.76 (95% CI 0.51–1.15), two-sided $P = 0.0879$. Median PFS was 10.9 and 8.3 months, respectively. In the cediranib 20 mg group, 40.5% of patients were event free at 12 months compared with 28.9% in the placebo group. The PFS comparison for cediranib 30 mg versus placebo was 0.96 (95% CI 0.64–1.46), two-sided $P = 0.429$. Median PFS was 9.8 and 8.3 months, respectively, and 36.1% of patients were event free at 12 months in the cediranib 30 mg group versus 28.9% in the placebo group.

At final data cut-off, 24 (41.4%), 27 (48.2%) and 23 (39.7%) patients had died in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. For the comparison of cediranib 20 mg versus placebo, the HR was 1.09 (95% CI 0.61–1.95), two-sided $P = 0.543$; median OS was not reached in the cediranib 20 mg group. For the comparison of cediranib 30 mg versus placebo, the HR was 1.28 (95% CI 0.73–2.24), two-sided $P = 0.706$. Median OS was 22.4 and 23.3 months in the cediranib 30 mg and placebo groups, respectively.

discussion

Patients enrolled in this study were representative of the target population of Japanese patients with previously untreated mCRC and consistent with previous studies [26, 27]. Although baseline characteristics were generally well balanced across the three groups, imbalances were noted. The imbalances in ALP and albumin levels probably occurred because the data were analysed at a central laboratory, whereas stratification according to baseline liver function was carried out in individual centres.

The median PFS of patients who received mFOLFOX6 alone in this study (8.3 months) was consistent with the SWIFT-2 (8.2 months) [27] and TREE-1 (8.7 months) [28] studies, in

which patients received mFOLFOX6 as first-line treatment of mCRC. Furthermore, the median PFS of patients in this study who received cediranib 20 mg plus mFOLFOX6 (10.2 months) compares well with the time to progression (9.9 months) for patients who received bevacizumab plus mFOLFOX6 in the TREE-2 study [28]. It is worth noting that TREE-2 was conducted in non-Japanese patients and there is a lack of phase III data for bevacizumab plus FOLFOX in the first-line setting in Japanese mCRC patients. A recent phase I/II study of first-line therapy comprising capecitabine plus oxaliplatin (XELOX) and bevacizumab in 64 Japanese patients with mCRC revealed a median PFS of 11 months, although the primary end points of this study were safety and ORR [29].

Here, the higher response rate observed in patients treated with cediranib 30 mg compared with the other arms did not translate into prolonged PFS, possibly due to differences in tolerability profiles of the cediranib arms. More patients in the cediranib 30 mg group experienced AEs (in particular, grade 3/4 diarrhoea) that led to discontinuation, dose reduction or dose interruption, than in the cediranib 20 mg or placebo groups. This appeared to impact on chemotherapy delivery—patients in the 30 mg arm received a lower dose intensity of oxaliplatin, which may reflect the differences in PFS outcomes. Due to these differences in tolerability, results from this study suggest that cediranib 20 mg is more suitable than 30 mg for long-term dosing in combination with mFOLFOX6 in Japanese patients with previously untreated mCRC. Cediranib 20 mg plus mFOLFOX6 was generally well tolerated, although the incidence of SAEs was higher compared with the placebo group. The most frequently reported AEs for the combination of cediranib 20 mg and mFOLFOX6 were diarrhoea and hypertension. The >50% incidence of palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome) in patients who received cediranib is consistent with a previous phase I study of cediranib monotherapy in Japanese patients and with studies of other targeted agents in Japanese patients with advanced cancer [30, 31]. Overall, no new safety issues were identified; no fatal AEs occurred and the AE profile was consistent with previous cediranib studies [10, 15]. With the exception of hypertension, diarrhoea, proteinuria, hypothyroidism, reversible posterior leukoencephalopathy syndrome, fatigue, hepatotoxicity, haematological toxicity and thrombocytopenia (for which specific management protocols were employed), cediranib-associated AEs were managed by dose interruption of up to 14 days or, if longer, treatment discontinuation. The incidences of grade ≥3 AEs and SAEs observed in this trial following addition of a TKI to FOLFOX therapy are consistent with those reported in trials involving vatalanib and bevacizumab in combination with a FOLFOX regimen [23, 32]. Cediranib treatment has shown a less favourable AE profile compared with bevacizumab in Western patients in the HORIZON III study [23]. In a phase I/II study in Japanese mCRC patients treated with XELOX plus bevacizumab, the most common grade 3/4 AEs were neurosensory toxicity (17%) and neutropenia (16%), both of which were managed by dose reduction of XELOX components; the incidence of grade 3/4 diarrhoea was only 3% [29]. It is not clear why the toxicity profiles of cediranib and bevacizumab differ, but it is probably related to differences in mechanism of action; cediranib is a potent inhibitor of the three VEGF receptor tyrosine kinases, whereas the activity of bevacizumab is dependent on preventing VEGF from binding to VEGF receptors, rather than blocking the receptors directly. In addition, the potential contribution of cediranib activity versus non-VEGFR kinases, e.g. c-Kit inhibition [33], cannot be excluded. Furthermore, cediranib undergoes extensive metabolism, so it is possible that one or more metabolites may add to the toxicity profile.

An assessment of the levels of the soluble biomarkers VEGF and sVEGFR-2 was conducted as an exploratory objective. Owing to the limited data, caution should be taken when drawing conclusions from these findings; however, the observed increase in VEGF levels and decrease in sVEGFR-2 levels in cediranib-treated patients are consistent with previous cediranib trials [10, 21]. The increased VEGF levels may represent an acute stress response to inhibition of VEGF signalling by cediranib, whereas changes in sVEGFR-2 levels could be a surrogate marker for biological activity.

Analysis with an additional 8 months of follow-up data revealed similar findings to the pre-specified protocol analysis in both efficacy and safety outcomes. This additional analysis confirmed that PFS in this study (HR = 0.76) is consistent with the HORIZON II study (HR = 0.84), in which significantly improved PFS was observed with the addition of cediranib 20 mg to standard chemotherapy (FOLFOX/XELOX) [22].

This study met its primary end point for improved PFS with cediranib 20 mg plus mFOLFOX6 compared with placebo plus mFOLFOX6. The outcomes from this study, and from HORIZON II [22] and HORIZON III [23], provide some understanding of the potential role of VEGFR TKIs in the management of previously untreated mCRC. In unselected patient populations, cediranib provided marginal clinical benefit when added to standard oxaliplatin-based chemotherapy. These data did not support further development of cediranib in CRC; however, further investigation may reveal a particular benefit in a more selective patient population.

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disclosure

KY has received speaker fees (Merk Serono and Chugai Pharmaceutical). XS and KF are employees of AstraZeneca and own stock. All other authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE – PANCREATIC TUMORS

Perioperative Intra-Arterial and Systemic Chemotherapy for Pancreatic Cancer

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ABSTRACT

Background. Even after curative resection of pancreatic cancer, there is a high probability of systemic recurrence. This indicates that subclinical metastases are already present at the time of operation. The purpose of this study was to assess the feasibility and outcomes of patients who received a novel multimodality therapy combining pancreatic resection and intraoperative radiation therapy (IORT) with pre- and postoperative chemotherapy for pancreatic cancer.

Methods. For eligible patients with pancreatic cancer, 5-FU was administered at a dose of 125 mg/m^2/day on days 1–5 every week as a continuous pancreatic and hepatic arterial infusion, and gemcitabine was infused intravenously at a dose of 800 mg/m^2 per day once per week for 2 weeks for preoperative chemotherapy. Pancreatic resection combined with IORT was performed 1 week after preoperative chemotherapy. Postoperative chemotherapy was performed in the same way as preoperative chemotherapy. We performed an intention-to-treat analysis for all enrolled patients.

Results. This study enrolled 44 patients. The most common toxicities were hematological and gastrointestinal events. Grade 3/4 hematological toxicities were observed during preoperative chemotherapy, although there were no grade 3/4 nonhematological events. Postoperative chemotherapy-related toxicities were more critical and frequent than preoperative ones. There were no pre- or postoperative chemotherapy-associated deaths. Median overall survival was 36.5 months with 30.5% overall 5-year survival.

Conclusions. This multimodality therapy is feasible and promises to contribute to survival. It should be evaluated in a phase III setting.

Pancreatic adenocarcinoma remains a lethal disease, with an overall 5-year survival rate ranging from 0.4 to 5%.[1,2] Even after curative resection of pancreatic cancer, there is a high probability of systemic and/or local recurrence.[3–5] This indicates that subclinical metastases are already present in most patients at the time of operation, even if preoperative radiological imaging or intraoperative examination revealed no metastatic lesions. Therefore, a multimodality strategy, including not only local control but also treatment of micrometastases, is required for patients with pancreatic cancer. For local control, beginning in 1984 we introduced extended radical pancreatectomy combined with intraoperative radiation therapy (IORT).[6] This approach provided the best control of local recurrence, but there was no survival benefit because of blood-borne metastases.[5] To treat unresectable pancreatic cancer, we introduced a combination of chemotherapy using 5-fluorouracil (5-FU) pancreatic and hepatic arterial continuous infusion and systemic gemcitabine administration; this combined therapy was well tolerated, with a 1-year survival rate of 50.9%.[7]

We studied a novel multimodality therapy combining pancreatic resection and IORT with pre- and postoperative chemotherapy using 5-FU intra-arterial continuous infusion and systemic gemcitabine administration in patients with potentially resectable pancreatic cancer. The purpose of this study was to evaluate the feasibility and outcomes of this multimodality therapy.

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PATIENTS AND METHODS

Patients

All patients were advised of the investigational nature of the study and gave their written, informed consent to participate before the beginning of the study. All patients underwent a standard pretreatment evaluation that included a physical examination, a thin-section, contrast-enhanced, multiphase spiral computed tomography (CT) of the abdomen, and ultrasonography. The absence of liver metastasis was confirmed by CT during arterial portography combined with CT-assisted hepatic arteriography (CTAP + CTHA), as described previously.[8] The absence of lung metastasis was confirmed by chest CT. The protocol required patients with potentially resectable disease as assessed by a physical examination and the following objective radiographic criteria: (1) no evidence of remote metastases; (2) no evidence of tumor extension to the celiac axis or the superior mesenteric artery. We included only patients in whom it was technically possible to resect and reconstruct the superior mesenteric vein (SMV) or the portal vein (PV), if the tumor involved SMV or PV. We excluded cases in which the tumor was 1 cm or smaller in diameter, because of the very low possibility of systemic spreading of the disease. Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤ 2.

Perioperative Chemotherapy

The treatment schema is shown in Fig. 1. The pre- and postoperative chemotherapy consisted of the combination of 5-FU arterial continuous infusion and systemic gemcitabine administration. In all cases, the catheter for arterial infusion was introduced from the femoral artery under local anesthesia. After the closure of the distal tip of the catheter, a side hole was made at an appropriate site in the celiac axis to allow the distribution of 5-FU to both the pancreatic tumor and the liver preoperatively, and in the hepatic artery to distribute the drug to the whole liver postoperatively. An arterial port was implanted in the subcutaneous tissue. 5-FU was administered at a dose of 125 mg/m^2 per day on days 1–5 each week as continuous infusion through the arterial port for 2 weeks during preoperative chemotherapy and for 8 weeks during postoperative chemotherapy. Gemcitabine was infused intravenously for 30 min at a dose of 800 mg/m^2 once weekly for a total of 2 doses preoperatively and for a total of 18 doses postoperatively. The doses of these drugs were based on our preliminary results for the combination chemotherapy using 5-FU intra-arterial infusion and systemic gemcitabine for unresectable pancreatic cancer.[7]

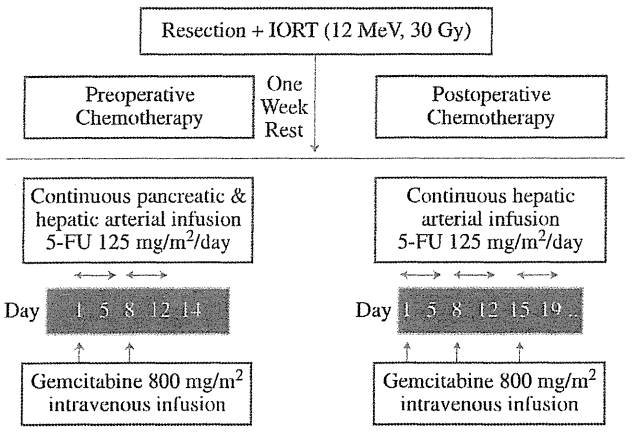

FIG. 1 Treatment schema. 5-FU was administered on days 1–5 every week as a continuous arterial infusion combined with gemcitabine infused once weekly for 2 weeks followed by pancreatic resection combined with IORT. Postoperative chemotherapy was performed in the same way as preoperative chemotherapy

In cases of grade 3 or higher toxicity according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0, drug infusion was interrupted until recovery. History, physical examination, and complete blood counts (CBCs) were repeated weekly before infusion of the drugs. Chemistry profiles were performed every 2 weeks. The catheter and port for arterial infusion were removed after the completion of intra-arterial infusion of 5-FU.

Surgery

Patients with cancer of the head of the pancreas underwent a substomach-preserving pancreaticoduodenectomy (SSPPD), a pylorus-preserving pancreaticoduodenectomy (PPPD), or a Kausch-Whipple resection: the last of these was performed if a tumor directly invaded the duodenum or antrum of the stomach, or if a distal gastrectomy had been performed before. Patients with cancer of the body or tail of the pancreas underwent a distal pancreatectomy. Patients underwent resection with reconstruction of SMV or PV if a tumor was thought during surgery to involve these vessels. For IORT, a dose of 30 Gy with a 12 MeV of electron beam was delivered to the operative field using a special pentagon applicator following dissection, as described previously.[6]

Hospital death was defined as death during hospitalization. Major surgical complications included any occurrence of anastomotic leak, postoperative intra-abdominal or gastrointestinal hemorrhage or fistula, intra-abdominal abscess, pneumonia, catheter-related sepsis, thromboembolic events, and reoperation. Pancreatic fistula was assessed according to an international study group (ISGPF) definition.[9]

Toxicity and Outcome Evaluation

Toxicities were graded according to NCI-CTC version 3.0. Survival was calculated from the day of surgery and estimated by the Kaplan–Meier method. The first site of disease recurrence was documented for outcome analysis.

All patients were evaluated every 3–4 months by physical examination as well as by chest and abdominal CT after surgery. For those without any recurrence after 2 years, follow-up was at 6-month intervals. Cytologic or histologic confirmation of disease recurrence was not required.

RESULTS

Patient Characteristics

From May 2001 through September 2008, 44 patients were enrolled in this study. The patients' characteristics are outlined in Table 1. The primary pancreatic lesion was located in the head in 33 patients, in the body in 9, and in the tail in 2. All patients underwent pancreatic resection. Pancreatic ductal adenocarcinoma was confirmed in all patients histologically. R0 resection was performed in 37 patients, R1 resection in 5 (11.4%), and R2 resection in 2 (4.5%). The median tumor size was 3 (range, 1.3–8.7) cm. Lymph node metastases were identified in 30 patients (68.2%), including para-aortic lymph node metastases in 3 patients. Resection and reconstruction of SMV or PV were necessary in 22 patients (50%), although 13 (29.5%) were proven to have histological portal invasion. Thirty-four patients received IORT after resection. All of the patients began postoperative chemotherapy after recovery from surgery, although 20 patients (45.5%) were completely treated according to the postoperative schedule. The mean pre- and postoperative doses of total 5-FU administered per patient were 2.8 and 5.2 g. The mean pre- and postoperative doses of total gemcitabine were 5.2 and 14.3 g.

Toxicities of Pre- and Postchemotherapy and Surgery

All 44 patients were included in the toxicity analysis. The overall toxicity profiles related to pre- and postoperative chemotherapy are outlined in Table 2. The most common toxicities were hematological and gastrointestinal events.

Nineteen patients (43.2%) experienced grade 3/4 neutropenia during preoperative chemotherapy. All preoperative chemotherapy-related toxicities abated after discontinuation of drug infusion. Forty-three patients underwent surgery 1 week after the completion of preoperative chemotherapy. Only one patient experienced a delay in surgery because of grade 4 neutropenia. Five major complications occurred in five patients after surgery, including grade C pancreatic fistula in two patients, intra-abdominal abscess in one, and cerebral infarction in one. Three patients recovered from complications by means of conservative therapies. One patient underwent reoperation for grade C pancreatic fistula. Hospital death was observed in one patient because of liver failure after intra-abdominal bleeding caused by pancreatic fistula.

TABLE 1 Patient characteristics

Characteristics	No. of patients	%
Total no. of patients	44	
Median age (yr)	65 (37–79)	
Male/female	26/18	
Site of primary lesion		
Head	33	75
Body	9	20.5
Tail	2	4.5
Pancreatectomy		
PPPD	16	36.4
SSPPD	13	29.5
PD	4	9.1
DP	11	25
Stage		
Ia	3	6.8
Ib	1	2.3
IIa	10	22.7
IIb	26	59.1
III	1	2.3
IV	3	6.8
Histologic differentiation		
Well	16	36.4
Moderately	22	50
Poorly	5	11.4
Adenosquamous	1	2.3
Tumor size (cm)		
1.0–2.0	6	13.6
2.1–4.0	33	75
>4.1	5	11.4
Nodal involvement		
Present	30	68.2
Absent	14	31.8
Portal vein invasion		
Present	13	29.5
Absent	31	70.5
Residual tumor		
R0	37	84.1
R1	5	11.4
R2	2	4.5

PPPD pylorus-preserving pancreaticoduodenectomy; *SSPPD* substomach-preserving pancreaticoduodenectomy; *PD* pancreaticoduodenectomy; *DP* distal pancreatectomy

TABLE 2 Pre- and postoperative chemotherapy-related grade 3/4 toxicities

	Preoperative	Postoperative
Hematological		
Anemia	0	4 (9.1)
Leukopenia	8 (18.2)	14 (31.8)
Neutropenia	19 (43.2)	24 (54.5)
Thrombocytopenia	2 (4.5)	3 (6.8)
Others		
Perforation of small intestine	0	1 (2.3)
Liver abscess	0	3 (6.8)
Cardiac ischemia/infarction	0	2 (4.5)
Renal dysfunction	0	1 (2.3)
Cholangitis	0	3 (6.8)
Appetite loss	0	1 (2.3)

Percentages are shown in parentheses

Toxicities are defined by NCI-CTC for Adverse Events v3.0

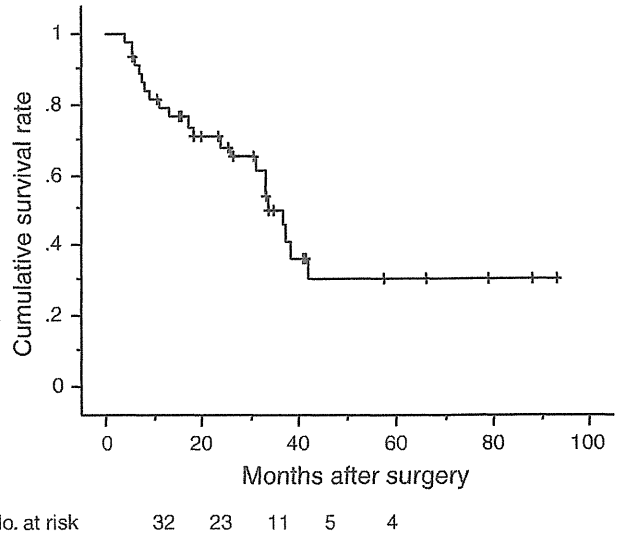

FIG. 2 Overall survival curve for all patients

Postoperative chemotherapy was initiated between 3 and 12 weeks after surgery. Twenty-four patients (54.5%) experienced grade 3/4 neutropenia during postoperative chemotherapy, although these toxicities abated after drug infusion was interrupted. Perforation of the small intestine in one patient occurred 1 year after pancreatic resection. This patient underwent emergency surgery and recovered. Grade 3/4 cardiac ischemia occurred in two patients and liver abscess in three patients (6.8%) during postoperative chemotherapy. No intra-arterial catheter-related toxicity occurred in any of the patients. Neither pre- nor postoperative chemotherapy-associated death was observed.

Survival and Outcome

The median follow-up period was 28.2 (range, 5.5–93.3) months. The 1, 3, and 5-year actuarial overall survival rates in all the patients were 78.8, 50.3, and 30.5%, respectively (Fig. 2). The median survival time was 36.5 months.

At last follow-up, 22 of the 44 patients (50%) had died. Seventeen (38.6%) had died as a result of recurrence. There were five (11.4%) non-cancer-related deaths, including one hospital death. Twenty-two patients (50%) remained alive. The median time of tumor recurrence was 24.0 months from the day of surgery. Liver metastases were observed in four patients (9.1%), peritoneal dissemination in six (13.6%), lung metastases in one (2.3%), pleural dissemination in one, bone metastases in one, and local recurrence in four (Table 3). Eight patients survived more than 32.3 months. The two patients with R2 resection died of peritoneal dissemination within 12 months.

TABLE 3 Outcomes after this multimodality therapy for patients with pancreatic cancer

	No.
Cancer deaths	17
Liver metastases	4
Lung metastases	1
Pleural dissemination	1
Peritoneal dissemination	6
Local recurrence	4
Bone metastases	1
Non-cancer-related deaths	5
Alive	22
Total	44

DISCUSSION

To our knowledge, this is the first report of perioperative intra-arterial and systemic chemotherapy for pancreatic cancer. This treatment was clearly operator-dependent. Grade 3/4 neutropenia was relatively frequent during perioperative chemotherapy, although the toxicities abated after interruption of drug infusion. Grade 3/4 nonhematological toxicities were observed during postoperative chemotherapy. Liver abscess occurred in three patients. This was thought to be influenced by regurgitated cholangitis, because all of the patients underwent hepaticojejunostomy after PD. Perforation of the small intestine occurred in one patient 3 months after completion of postoperative chemotherapy. Cardiac ischemia required hospitalization for two patients. However, the relationship between these events and chemotherapy was unclear. Toxicities were more critical and frequent during postoperative chemotherapy than during preoperative. Intra-arterial infusion was acceptable

for perioperative chemotherapy, because no catheter-related toxicity was observed.

Practical and theoretical advantages of preoperative treatment of pancreatic cancer were proposed as an early treatment for micrometastases and optimized patient selection for surgery.[10–12] Circulating tumor cells in the blood proved to be present in 28% of patients with pancreatic cancer, and the prevalence increased with tumor stages.[13] Moreover, complications, which occurred after 30–45% of major pancreatic resections, delayed the initiation of postoperative chemotherapy.[14,15] These are supported to introduce preoperative chemotherapy for pancreatic cancer.

The rationale for intra-arterial infusion of chemotherapeutic agents appears to be promising from the point of view of the drug-concentration response, because most liver metastases (>3 mm) have an arterial blood supply.[16,17] Locoregional adjuvant chemotherapy has been reported to have 3-year survival rates ranging from 48 to 54%, and lower recurrence rates of liver metastases ranging from 8 to 17% for pancreatic cancer compared with no-adjuvant studies.[3,4,18,19] This study also showed that liver metastases diminished to 9.1%, indicating that intra-arterial chemotherapy might be effective to prevent liver metastases.

We adopted pancreatic resection combined with IORT for local control in this series. Local recurrence was observed in only four patients (9.1%). Single-institution experiences suggest that local failure rates were lower in radiation groups (10–26%) than in no-radiation groups (50–80%).[20–24] This indicated that resection combined with IORT could provide good control of local recurrence.

Recently, a phase III randomized trial (CONCO 001 study) demonstrated that adjuvant gemcitabine significantly delayed the development of recurrence after resection of pancreatic cancer, with a median survival time of 22.1 months.[25] Evans et al. reported on a phase II trial of neoadjuvant gemcitabine-based chemoradiation for stage I/II pancreatic cancer.[26] The median survival time of 36.5 months in our study is similar to the 34 months in the Evans group trial despite a greater proportion of patients with node-positive (68.2%) and R2 resection (4.5%) in our study than in the Evans group trial. Because our perioperative chemotherapy is complicated, it will be necessary to clarify which adjuvant treatment is most effective for pancreatic cancer to simplify treatment.

In conclusion, this perioperative chemotherapy for pancreatic cancer is feasible and promises to contribute to survival. It should be evaluated in a phase III setting.

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Review

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Induction Chemotherapy with Docetaxel/ Cisplatin/5-Fluorouracil for Patients with Node-Positive Esophageal Cancer

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Key Words

Cisplatin · Docetaxel · Esophageal cancer · 5-Fluorouracil · Induction chemotherapy · Neoadjuvant chemotherapy · Node-positive esophageal cancer

Abstract

Background: Despite improvements in the surgical management of esophageal cancer, the prognosis of patients with lymph node metastases is still unsatisfactory. Recently, survival benefit of neoadjuvant or induction chemotherapy for patients with esophageal cancer has been highlighted. ***Methods:*** Efficacy and toxicity of induction chemotherapy for esophageal cancer were reviewed. In addition, our experience on modified docetaxel/cisplatin/5-FU (DCF) as induction chemotherapy was also demonstrated. The modified DCF consisted of 60 mg/m^2 of docetaxel on day 1, and 350 mg/m^2 of 5-FU and 6 mg/m^2 of cisplatin on days 1–5. Two courses have been administered as induction chemotherapy in 51 patients with node-positive esophageal cancer. Response was evaluated by RECIST v1.0 and changes in standardized uptake value by ^{18}F-fluorodeoxyglucose positron emission tomography. ***Results:*** Induction chemotherapy may be beneficial for node-positive esophageal cancer, although the consensus has not yet been established. A regimen of induction chemotherapy should have a high response rate and cisplatin/5-FU may be underpowered as an induction setting. DCF can be a candidate for the regimen of induction chemotherapy for esophageal cancer, although severe adverse events have been reported. Several modified regimens to reduce the toxicity have been reported. The response rate of our series was 61% and a significant decrease in standardized uptake values was observed after the induction chemotherapy. Although high-grade neutropenia was still observed with this regimen, neither treatment-related death nor delay in the following treatment was observed. ***Conclusions:*** Modified DCF can be a regimen of induction chemotherapy for node-positive esophageal cancer because of its high efficacy, although an adequate care for severe neutropenia is needed.

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Introduction

Long-term survival of patients with esophageal cancer has been improved during several decades, mainly owing to progress in surgical treatment. Squamous cell carcinoma of the esophagus often spreads through the lymphatic vessels and widespread lymph node metastases are frequently observed from the early stage of this disease. Therefore, an extended radical lymph node dissection, the so-called three-field dissection, has been established in Japan [1, 2]. The prognosis of patients with esophageal cancer has been improved according to the spread of such a radical surgery, although there has been no randomized study that demonstrated the superiority of three-field dissection compared to limited lymphadenectomy.

In spite of improved surgical techniques, the prognosis of patients with lymph node metastases is still unsatisfactory even when a curative resection was performed, especially in cases with three-field lymph node metastases or numerous node metastases. A recent randomized control trial has revealed that adjuvant chemotherapy improved disease-free survival of patients with node-positive esophageal cancer [3]. Thereafter, the other studies demonstrated that the prognosis of patients who were treated with neoadjuvant chemotherapy followed by surgery was superior to that of patients who underwent esophagectomy followed by chemotherapy [4] or treated with surgery alone [5]. According to these findings, recently, chemotherapy followed by esophagectomy has become one of the standard cares for patients with resectable esophageal cancer.

Induction chemotherapy is defined as chemotherapy as the initial treatment for cancer, especially as part of a combined modality therapy. In this meaning, neoadjuvant chemotherapy is included in this entity. However, there is another definition of induction chemotherapy that is defined as the use of drug therapy as the initial treatment for patients presenting with advanced cancer that cannot be treated by other means. According to this definition, neoadjuvant chemotherapy is apparently different from induction chemotherapy. In this article, efficacy and toxicity of induction chemotherapy as the former definition, including neoadjuvant chemotherapy, has been reviewed.

Indication for Induction Chemotherapy

Consensus of who should be treated with chemotherapy prior to surgery or the other definitive treatments has not yet been developed. It is well known that lymph node metastasis is one of the major prognostic factors of patients who underwent curative esophagectomy. The nationwide registry of esophageal cancer in Japan has revealed that the number of lymph node metastasis correlated with the prognosis [6]. In the report the survival rate of patients with 1–3 metastatic nodes was significantly lower than that of patients without nodal involvement. The 5-year survival rate of patients with 4–7 metastatic nodes was as low as 20% and that of patients with more than 8 metastatic nodes was miserable. These results indicate that node-positive cases are candidates for induction chemotherapy.

The Japanese Clinical Oncology Group (JCOG) has targeted patients with clinical stage II/III by TNM classification for their randomized trials concerning adjuvant chemotherapy, mentioned above. In JCOG 9204, adjuvant chemotherapy prolonged disease-free survival of patients with node-positive tumors, but no survival benefit was evident in patients without nodal involvement [3]. The result suggests that patients with node-positive tumors should be treated with adjuvant chemotherapy. On the other hand, in JCOG 9907, which compared preoperative chemotherapy with postoperative chemotherapy, survival benefit of preoperative chemotherapy was observed only in clinical stage II patients but not in stage III patients [4]. Nodal status did not affect the survival benefit of preoperative chemotherapy in this particular study.

Regimens Used for Neoadjuvant or Induction Chemotherapy

An optimal regimen of induction chemotherapy for esophageal cancer has not yet been established. Patients who are targeted by induction chemotherapy include cases with potentially curable tumors by surgery alone and thus they may lose the chance to be cured if tumor progression occurred during the chemotherapy. Therefore, a high response rate, or at least a high disease control rate is required for the regimen. On the other hand, as esophagectomy is a surgery with great surgical stress, a regimen which does not cause organ dysfunction or does not worsen patients' physical condition is desirable. Especially patients with squamous cell carcinoma of the esophagus are frequently accompanied by several organ disorders, because they are usually of high age and tend to have a long-term history of smoking and alcoholic use.

The combination of cisplatin and 5-fluorouracil (FP) has been a standard regimen for advanced or metastatic

Table 1. Response rate and pathological complete response rate of patients with esophageal cancer treated with neoadjuvant or induction chemotherapy

Reference (first author)	Regimen	Cases, n	Response rate, %	Pathological complete response rate, %
Schlag [7]	cisplatin/5-FU	22	50	–
Roth [8]	cisplatin/vindesine/bleomycin	19	47	–
Kelsen [9]	cisplatin/5-FU	233	19	2.5
Law [10]	cisplatin/5-FU	74	–	6.7
Ancona [11]	cisplatin/5-FU	48	–	12.8
Igaki [4]	cisplatin/5-FU	164	37.8	2.4
Shimakawa [12]	cisplatin/adriamycin/5-FU	27	55.6	7.4
Miyata [13]	cisplatin/adriamycin/5-FU	74	63.5	4.1
Current study	docetaxel/cisplatin/5-FU	51	60.8	11.1

esophageal cancer. As shown in table 1, many of the series on preoperative chemotherapy also used FP as their chemotherapeutic regimen [4, 7, 9–11]. However, it has not been established that FP is the best regimen for induction or neoadjuvant chemotherapy for patients with esophageal cancer. The major problem of this regimen is that the response rate is not high enough. The response rate of this regimen for advanced or metastatic esophageal cancer is reported to be less than 40% [14]. In a neoadjuvant setting, it has been reported to be 19–50% (table 1). These results indicate that FP may be underpowered as induction chemotherapy.

Recently, several regimens of combination chemotherapy for esophageal cancer have been reported such as cisplatin/paclitaxel [15], cisplatin/CPT-11 [16], and cisplatin/gemcitabine [17]. However, the efficacy of these regimens as induction chemotherapy has not yet been reported. On the other hand, triplet chemotherapy, which consisted of an addition of another drug to FP, has been focused. Adriamycin in addition to FP (FAP) has been reported as a candidate for neoadjuvant regimen for esophageal cancer. The response rate of FAP has been reported to be as high as 55.6 and 63.5%, while pathologic complete response rate was not so high (7.4 and 4.6%) [12, 13].

The only drug which has been proven to have an additional effect to FP by a randomized control trial is docetaxel. Docetaxel combined with FP (DCF) is now considered to be one of the standard regimens for gastric or esophagogastric adenocarcinomas [18]. DCF has also been reported to be effective as induction chemotherapy for head and neck squamous cell carcinoma, which has biologically similar features as esophageal squamous cell cancer [19]. Therefore, DCF is considered to be one of the most promising regimens of induction chemotherapy for esophageal cancer.

Adverse Events of DCF

A major problem of the DCF regimen is considered to be its high degree of adverse events. Especially high-grade neutropenia and febrile neutropenia are potentially life-threatening events. As shown in table 2, among patients who were treated with the original DCF regimen for gastric cancer, grade 3/4 neutropenia and febrile neutropenia was observed in 82 and 29%, respectively [18]. Similarly, grade 3/4 neutropenia was observed in 83% of patients who were treated with DCF as induction chemotherapy for head and neck cancer, while febrile neutropenia was seen in 12% [19]. Although it is unclear why the difference in rate of febrile neutropenia is observed between these two studies despite the similar rate of high-grade neutropenia, it may depend on the difference in site of cancers or condition of the patients. In order to reduce the toxicities, several modified regimens have been attempted (table 2) [20–25]. In many of these modified regimens, efforts have been focused on reducing dose of docetaxel per administration. There are a few regimens which used oxaliplatin instead of cisplatin [23, 24]. Owing to these modifications, both high-grade neutropenia and febrile neutropenia have been reduced, although there is no comparative study on the effectiveness.

Table 2. Rate of grade 3/4 neutropenia and febrile neutropenia in patients treated with DCF or modified regimens

Reference (first author)	Regimen	Target	Phase	Cases, n	Grade 3/4 neutropenia %	Febrile neutropenia %
Van Cutsem [18]	D: 75 mg/m^2 day 1 C: 75 mg/m^2 day 1 F: 1,000 mg/m^2 days 1–5	gastric cancer	III	221	82	29
Posner [19]	D: 75 mg/m^2 day 1 C: 100 mg/m^2 day 1 F: 1,000 mg/m^2 days 1–5	head and neck cancer	III	225	83	12
Park [20]	D: 50 mg/m^2 day 1 C: 80 mg/m^2 day 1 F: 1,200 mg/m^2 days 1–5	gastric cancer	II	47	68	26
Lorenzen [21]	D: 40 mg/m^2 days 1, 15, 29 C: 40 mg/m^2 days 1, 15, 29 F: 2,000 mg/m^2 weekly	gastric cancer	II	60	22	5
Tebbutt [22]	D: 30 mg/m^2 days 1, 8 C: 60 mg/m^2 day 1 F: 200 mg/m^2 days 1–5	esophagogastric cancer	II	49	–	4
Ajani [23]	D: 50 mg/m^2 day 1 O: 85 mg/m^2 day 1 F: 2,200 mg/m^2 days 1–2	gastroesophageal cancer	II	36	–	0
Al-Batran [24]	D: 50 mg/m^2 day 1 O: 85 mg/m^2 day 1 F: 2,600 mg/m^2 day 1	gastroesophageal cancer	II	53	48	2
Overman [25]	D: 20 mg/m^2 weekly C: 20 mg/m^2 weekly F: 350 mg/m^2 weekly	esophagogastric cancer	retrospective	95	4	0
Current study	D: 60 mg/m^2 day 1 C: 6 mg/m^2 days 1–5 F: 350 mg/m^2 days 1–5	esophageal cancer	II	51	84.3	15.7

D = Docetaxel; C = cisplatin; F = 5-fluorouracil; O = oxaliplatin.

DCF for Esophageal Cancer

There are a few studies that demonstrated the efficacy of DCF for patients with squamous cell carcinoma of the esophagus. On the other hand, induction chemotherapy using DCF for patients with esophageal cancer has never been reported. One of the reasons is that docetaxel has been graded as a second-line drug for tumors refractory to FP in Japan. A modified DCF (mDCF) regimen has also been reported as a second-line chemotherapy for patients with cisplatin-pretreated refractory esophageal cancer [26]. In the study, the regimen consisted of 60 mg/m^2 of docetaxel on day 1, given intravenously, 500 mg/day of 5-FU on days 1–5 as a 24-hour continuous intravenous infusion, and 10 mg/day of cisplatin, given intravenously on days 1–5. Although all of the patients assigned in the study had already received prior chemotherapy, they tolerated the mDCF well. Moreover, the response rate of the modified regimen was 35%, which was one of the highest rates as a second-line chemotherapy.

Efficacy of mDCF as Induction Chemotherapy for Esophageal Cancer

We have tried to figure out the efficacy and toxicity of mDCF as induction chemotherapy for patients with node-positive esophageal cancer. We used the regimen

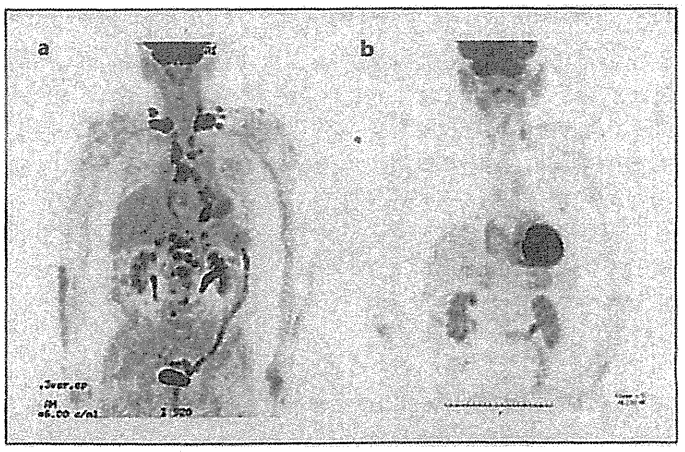

Fig. 1. Representative imaging of FDG-PET before (**a**) and after (**b**) induction chemotherapy. **a** Numerous tumors with FDG accumulation are observed in the neck, mediastinum and abdomen before chemotherapy. **b** FDG accumulation has disappeared after induction chemotherapy.

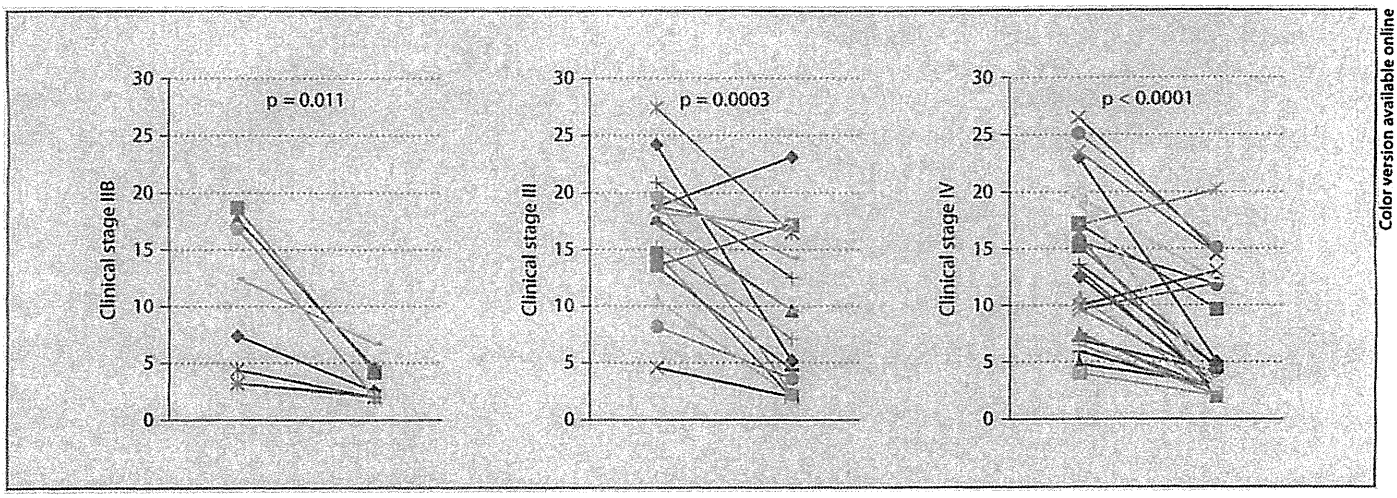

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Fig. 2. Changes in SUV during induction chemotherapy in the primary esophageal tumors. Significant decrease in SUV was observed by induction chemotherapy, irrespective of the staging.

according to the above-mentioned modified regimen. As shown in table 2, the regimen consisted of 60 mg/m^2 of docetaxel on day 1, given intravenously, 350 mg/m^2 of 5-FU on days 1–5 as a 24-hour continuous intravenous infusion, and 6 mg/m^2 of cisplatin, given intravenously on days 1–5. After two courses of chemotherapy, the response was evaluated by RECIST v1.0. The response rate of this regimen was 60.8%, which was comparable to that of FAP. Moreover, the pathological complete response rate was higher than those of the other regimens. There was no patient with progressive disease during two courses of induction chemotherapy.

Recently, the usefulness of ^{18}F-deoxyglucose positron emission tomography (FDG-PET) in determining the effect of chemotherapy or CRT for several kinds of malignancies has been reported [27]. The standardized uptake value (SUV) in FDG-PET has been reported to reflect the biological activity of tumors and therefore response to treatment can be estimated by changes in the SUV. Representative imaging of FDG-PET before and after induction chemotherapy with mDCF is shown in figure 1. Multiple nodules with uptake of FDG were observed in the neck, mediastinum and abdomen, suggesting esophageal cancer with extended lymph node metastases (fig. 1a). After two courses of mDCF, uptakes of FDG have disappeared (fig. 1b). A complete response was achieved by CRT after the induction chemotherapy in this case. Changes in SUV of the primary esophageal tumors by

induction chemotherapy are shown in figure 2. A decrease in SUV was observed in 46 of 51 patients (90.2%). When we look at the changes in SUV in each clinical stage, a decrease in SUV was observed in 8/8 (100%), 14/16 (87.5%), and 23/26 (88.5%) in stage IIB, III and IV, respectively. These results indicate that the mDCF regimen is highly effective as induction chemotherapy for patients with node-positive esophageal cancer, irrespective of the staging.

Toxicity of mDCF as Induction Chemotherapy for Esophageal Cancer

On the other hand, hematologic toxicity of this regimen was still severe, although non-hematologic adverse events were mild enough to carry out two courses of chemotherapy without any delay in all 51 cases. The major problem is febrile neutropenia observed in 15.4% of the patients, as shown in table 2. Although the rate was almost 10% less than that of the original DCF regimen for gastric cancer and there was neither treatment-related death nor delay in the treatment, further efforts to reduce the harmful toxicity are needed. As the severe neutropenia is probably dependent on a dose of docetaxel, the simplest way to reduce the toxicity is to reduce the dose of docetaxel, whereas the dose reduction may have a risk to negatively affect the efficacy. Recently, the significance of secondary prophylaxis against febrile neutropenia has been reported when chemotherapy with a high risk of neutropenia was performed. As the duration of neutropenia induced by docetaxel is short, and rapid recovery of neutrophil is usually observed within a few days, secondary prophylaxis may be useful in the DCF regimen.

Conclusions

Induction chemotherapy may be beneficial for patients with advanced esophageal cancer. DCF can be a candidate for the regimen of induction chemotherapy because of its high antitumor activity. A mDCF regimen is tolerable as induction chemotherapy, although an adequate care for febrile neutropenia is needed.

Disclosure Statement

The authors declare that no financial or conflict of interest exists in relation to the contents of the article.

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Case Report

Successful Treatment of Cisplatin Overdose with Plasma Exchange

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Accidental cisplatin overdose has been occurring with an increasing frequency due to expanding usage of the agent. However, the optimal strategy to treat such patients remains to be established. Here, we report a case of large cisplatin overdose, successfully managed by plasma exchange, intravenous hydration, granulocyte colony-stimulating factor (G-CSF) administration, and other supportive care. A 67-year-old man with esophageal carcinoma received a large cisplatin overdose of 240 mg/m^2, when he received adjuvant therapy following subtotal esophagectomy. On day 4, he experienced frank cisplatin toxicities and emergency plasma exchange was initiated. With 7 cycles of plasma exchange, the cisplatin concentration decreased from 2,350 to 110 ng/mL. Severe bone marrow suppression with high fever ensued on day 10, which was successfully treated with G-CSF and antibiotics. Despite moderate hearing sense reduction, he recovered without significant complications. Immediate plasma exchange with hydration and other care was efficacious in quickly lowering cisplatin concentrations.

1. Introduction

Cis-diamminedichloroplatinum (II) (cisplatin) represents one of the most widely used and effective antineoplastic agents. The heavy metal platinum causes interstrand cross-linking of DNA, thereby preventing tumor cell proliferation [1]. Preclinical data suggest that cisplatin has a steep dose-response relationship for ovarian cancer and other tumors [2]. However, despite vigorous intravenous hydration and mannitol treatment, acute nephrotoxicity and chronic renal damage often occur after administration of therapeutic doses of cisplatin, 100 to 120 mg/m^2 per one cycle of chemotherapy [3]. In particular, higher doses of cisplatin due to accidental overdose have been reported to cause nephrotoxicity, neurotoxicity, ototoxicity, gastrointestinal disturbances, and severe myelosuppression [4]. Although there are reports describing that patients receiving massive cisplatin overdose were successfully rescued [4–8], the optimal strategy to treat overdosed patients remains to be established.

Here, we report a 67-year-old man who suffered an accidental cisplatin overdose of 240 mg/m^2. Although the patient was left with moderately reduced sense of hearing, he ultimately recovered without significant complications with plasma exchange combined with intravenous hydration, G-CSF administration, and other supportive care.

2. Case Report

A 67-year-old man was diagnosed with stage II esophageal carcinoma (T1N2M0). Endoscopic examination showed a white plaque lesion spreading from 35 to 37 cm from incisors after spraying of Lugol's iodine solution. No spread beyond the adventitia was apparent with both computed tomography (CT) and positron emission tomography examinations. However, metastatic lymph node involvements in regions I and III were noted. Histopathology revealed well-differentiated squamous cell carcinoma. He underwent subtotal esophagectomy and was diagnosed to be at post-operative stage IIIa (pT3N3M0). He subsequently received postoperative adjuvant chemotherapy. The patient was put in a treatment protocol consisting of cisplatin 80 mg/m^2 on day 1 and 5-fluorouracil (5-FU) 800 mg/m^2 from days 1 to 5.

However, he was inadvertently administered with cisplatin 80 mg/m^2 plus 5-FU 800 mg/m^2 for consecutive 3 days, which fell upon Saturday, Sunday, and a national holiday in Japan. On day 4, which was Tuesday, the patient complained that he had hearing difficulty, and the cisplatin overdose was noted, and further chemotherapy was disrupted (Figure 1(a)). The patient was immediately transferred into a laminar flow clean room. Ototoxicity, nonoliguric renal failure, hepatic dysfunction, and acute pancreatitis were identified. Laboratory test revealed his BUN of 40.2 mg/dL, creatinine 1.99 mg/dL (175.9 μM/L), AST 251 U/L, ALT 229 U/L, total bilirubin 0.6 mg/dL, amylase 178 U/L, and LDH 445 U/L. Hemodialysis and detoxification with sodium thiosulfate (STS) were performed on the same day and emergency plasma exchange was implemented on day 5 (Figure 1(a)).

His plasma and urine total platinum concentrations were examined with flameless Zeeman atomic absorption spectrophotometry using Simultaneous Multielement Atomic Absorption Spectrometer 6000 (PerkinElmer. Inc., MA, USA). His plasma cisplatin concentration was 2,350 ng/mL after a cycle of hemodialysis and treatment with STS. On days 5 through 19, the patient underwent plasma exchange seven times and his plasma cisplatin concentration decreased to 110 ng/mL (Figure 1(a)). It was noted that his plasma cisplatin concentration was abruptly decreased after 2 cycles of plasma exchange; however, despite daily plasma exchange conducted, an increase of cisplatin concentration was observed twice, on days 8 and 10 (Figure 1(a)).

His cisplatin excretion in urine was 4.8 mg/day on day 6. Of note, on day 15, when his plasma cisplatin concentration dropped below 180 ng/mL, cisplatin excretion in his urine yet persisted from 1.5 mg/day to 1.8 mg/day. On day 12, severe leukocytopenia occurred and the administration of granulocyte colony stimulating factor (G-CSF) was implemented. Leukopenia was noted on days 10–13 with WBC counts of ~2,000/mL and slowly worsened afterward. On day 14, he developed high fever with infectious focuses unknown and his granulocyte counts were of ~10/μL, which persisted over 3 days despite the G-CSF administration (Figure 1(a)). Administration of broad-spectrum antibiotics (vancomycin and meropenem) was begun and his fever resolved by day 21. The patient was kept on fasting until day 19 because of mucositis that was thought to have resulted from cisplatin overdose and bacterial infection.

After undergoing seven cycles of plasma exchange, his creatinine levels fell to 1.8 mg/dL (159.1 μM/L) and his creatinine clearance got stabilized at 35 mL/minute. His serum levels of AST, ALT, and amylase were 240 U/L, 280 U/L, and 527 U/L, respectively, as examined on day 5; however, they became normal by day 10. He slowly recovered from his initial hearing loss, and after a month he subjectively did not perceive distinct ototoxicity. However, when his auditory acuity was evaluated, a significant acuity reduction was noted at high frequency ranges. His left/right auditory acuity levels were 20/35, 40/30, 30/30, 60/55, and 80/75 dB at 500, 1,000, 2,000, 4,000, and 8,000 Hz (normal auditory acuity levels are between 0–20 dB at each range: the greater the value, the more compromised the hearing acuity).

His general conditions slowly but steadily improved without any further life-threatening complications arising from the cisplatin overdose and he was transferred into a general ward on day 28. Then, he was discharged later because of the eating disorders due to an esophageal stricture.

3. Discussion

Toxicities of cisplatin include emesis, nephrotoxicity, neurotoxicity, hearing loss, visual impairment, cholestasis, gastrointestinal disturbances, and bone marrow suppression [2]. The most serious complication is nephrotoxicity, which may result in irreversible renal failure [9, 10]. Patients inadvertently receiving less than 300 mg/m^2 of cisplatin reportedly often recover, whereas overdoses exceeding 400 mg/m^2 frequently result in death [2–7, 9, 11] (Table 1). As the toxicity of cisplatin is dose-dependent, early elimination of the drug from plasma should be critical in the management [12].

Reportedly, most of the platinum in the blood plasma is bound to proteins within a few hours after intravenous administration [4, 13]. The binding of cisplatin to proteins reduces urinary excretion of platinum and causes deposition of platinum in tissues. Binding of cisplatin to proteins and enzymes is generally believed to be the cause of its side effects, especially ototoxicity and nephrotoxicity. The protein-bound form cisplatin cannot be removed by hemodialysis [2, 4, 8, 14, 15]. Thus, hemodialysis is not effective in removing the protein-bound platinum; however, plasma exchange has been thought to be efficacious in treatment of cisplatin overdose. Indeed, in the present case, the plasma cisplatin concentration was as high as 2,350 ng/mL after one cycle of hemodialysis on day 4, while the plasma cisplatin concentration had decreased to 360 ng/mL after two cycles of plasma exchange (Figure 1(a)). Paradoxically, an increase of plasma cisplatin concentration was observed twice, on days 8 and 10 despite of daily plasma exchange conducted. These results suggest that cisplatin deposited in tissues and intracellular cisplatin [2, 6] were being continuously released to plasma. It is noteworthy that afterwards his plasma cisplatin concentration slowly but constantly decreased. It is argued as to how many cycles of plasma exchange are required to sufficiently decrease cisplatin to nontoxic levels. Therefore, we believe that early and continuous plasma exchange is useful in the management of cisplatin overdose.

A number of thiols, including N-acetylcysteine, STS, and mesna, all of which bind to circurating reactive cisplatin derivatives, have been studied as chemoprotectants [7, 9]. These protectants are given before or during the administration of cisplatin.

In the present case, STS was administered on day 4; however, the efficacy of the administration in the present case is unclear [11]. Erdlenbruch et al. demonstrated that STS administrated 70 hours after an overdose had an effect in improving renal functions [7]. Nevertheless, there is no or little evidence that chemoprotectants can reverse hearing loss [16]. Moreover, it is of note that the use of chemoprotectant

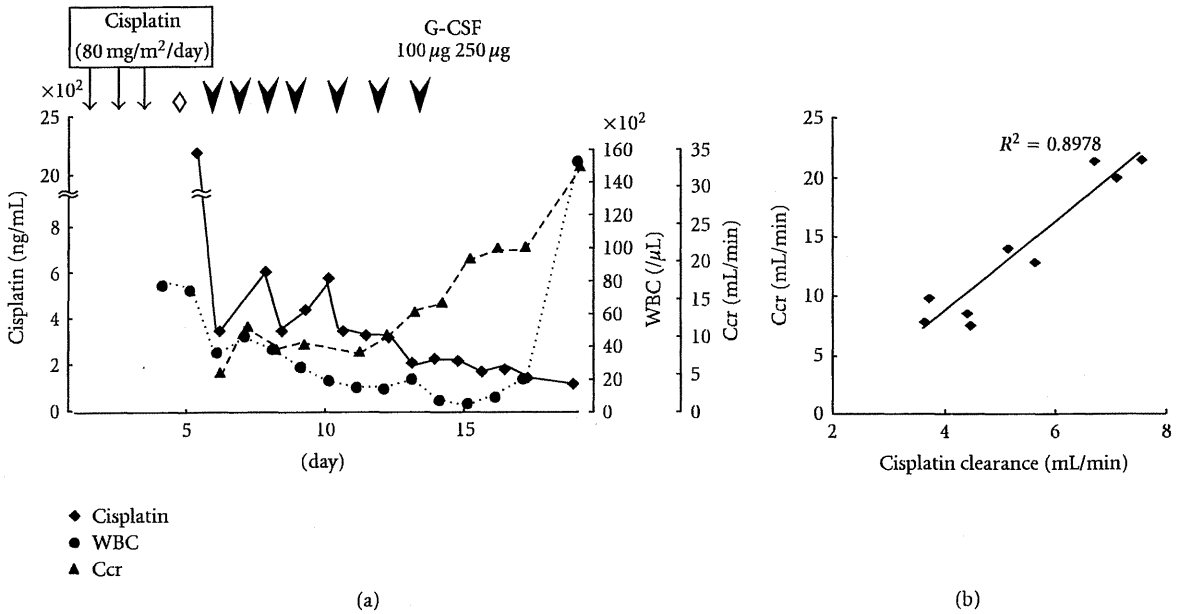

FIGURE 1: *Plasma cisplatin concentrations, leukocyte counts, Ccr values and platinum clearance values.* (a) An open diamond and arrow heads denote for dialysis and plasma exchange, respectively. (b) Note that cisplatin clearance approximately correlated with Ccr. WBC: white blood cell, G-CSF: granurocyte-colony-stimulating factor, Ccr: creatinine clearance.

TABLE 1: Selected literature of cisplatin overdose; PE: plasma exchange; HD: hemodialysis. STS: sodium thiosulfate.

Authors	Dose of cisplatin	Treatment	Outcome
Schiller et al.	480 mg/m²	PE, HD	Alive, irreversible hearing loss
Chu et al.	280 mg/m²	PE, HD	Alive, irreversible hearing loss
Lagrange et al.	205 mg/m²	HD	Alive
Jung et al.	300 mg/m²	PE	Alive
Sheikh-Hamad et al.	400 mg/m²	N-acetylcysteine	Dead
Choi et al.	400 mg/m²	PE, HD	Alive
Erdlenbruch et al.	360 mg/m²	STS	Alive
Charlier et al.	750 mg/body	PE, HD, N-acetylcysteine	Dead
Hofmann et al.	225 mg/m²	PE	Alive
Our patient	240 mg/m²	PE, HD, STS	Alive

alone may impose overload to the kidney of patients since the elimination of cisplatin mostly occurs through the kidney, whose functions may have already been compromised by the toxicity of the agent.

As shown in Figure 1(b), the platinum clearance of the patient, which was calculated as platinum excreted per minutes divided by plasma platinum concentration, approximately correlated with creatinine clearance (Ccr). Significant amounts of platinum were excreted in the urine. While the plasma cisplatin concentration was as low as <180 ng/mL, the amounts of cisplatin excreted into urine were persistently >1.5 mg/day after Ccr was improved. Thus, in removing cisplatin as quickly as possible, sufficient hydration should be continued and Ccr levels should be cautiously monitored even after plasma cisplatin concentrations became apparently within or close to normal ranges.

In the present case, we withheld the use of G-CSF until day 12, when the patient developed leucopenia. It is argued as to whether the administration of G-CSF should be implemented as soon as cisplatin overdose is revealed [6]. It is possible that stimulating hematopoietic cells to proliferate in the presence of toxic agents results in more substantial damage of such cells. It is known that certain anticancer agents such as cytarabine exert greater toxicity to granulocytes and granulocytic tumor cells when used with G-CSF [17]. Antiviral activity against human immunodeficiency virus of a nucleoside analogue, azidothymidine, is also potentiated in macrophages/monocytes when such cells are stimulated by granulocyte-macrophage-colony stimulating factor (GM-CSF) [18]. Another reason we withheld the use of G-CSF in the present case was that the patient had sufficient numbers of granulocytes and no signs of infections for a week after

cisplatin overdosing, and we thought the administration of G-CSF was unnecessary. Indeed, G-CSF was started on day 12, when the patient had developed substantial leucopenia when his plasma platinum concentration had decreased from its peak to 210 ng/mL.

Upon cisplatin overdose, the attempt of immediate, continuous, and sufficient removal of the drug is an important factor for the management of the overdose. In the present case, adverse events resulting from the overdose were successfully treated with vigorous plasma exchange combined with G-CSF administration and other supportive care. In order to prevent the recurrence of such an accident, it cannot be overemphasized that rigorous check systems and careful monitoring are essential when patients are treated with cytotoxic therapeutics.

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