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

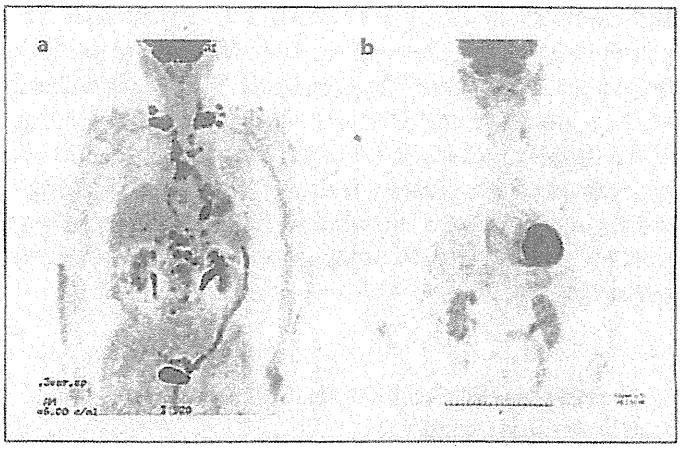

Fig. 1. Representative imaging of FDG-PET before (**a**) and after (**b**) induction chemotherapy. **a** Numerous tumors with FDG accumulation are observed in the neck, mediastinum and abdomen before chemotherapy. **b** FDG accumulation has disappeared after induction chemotherapy.

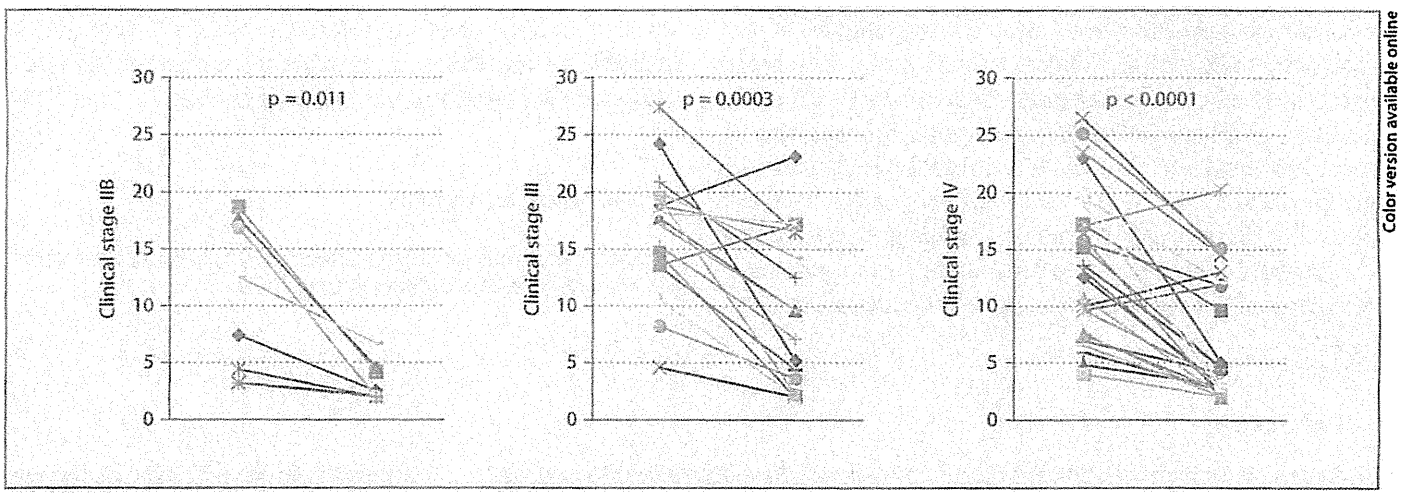

Fig. 2. Changes in SUV during induction chemotherapy in the primary esophageal tumors. Significant decrease in SUV was observed by induction chemotherapy, irrespective of the staging.

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.

References

1 Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y: Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364–373.
2 Fujita H, Kakegawa T, Yamana H, Shima I, Toh Y, Tomita Y, Fujii T, Yamasaki K, Higaki K, Noake T, Ishibashi N, Mizutani K: Mortality and morbidity rates, postoperative course, quality of life and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. Ann Surg 1995;222:654–662.
3 Ando N, Iizuka T, Ishida K, et al: Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study – JCOG9204. J Clin Oncol 2003;21:4592–4596.
4 Igaki H, Kato H, Ando N, Shinoda M, Shimizu H, Nakamura T, Ozawa S, Yabusaki H, Aoyama N, Kurita A, Fukuda H: A randomized trial of postoperative chemotherapy with cisplatin and 5-fluorouracil versus neoadjuvant chemotherapy for clinical stage II/III squamous cell carcinoma of the thoracic esophagus (JCOG9907). J Clin Oncol 2008; 26(suppl 215):4510.
5 Allum W, Stenning SP, Clark PI, Langley RE: Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062–5067.
6 Ozawa S, Tachimori Y, Baba H, Matsubara H, Muro K, Numasaki H, Oyama T, Shinoda M, Takeuchi H, Tanaka O, Teshima T, Udagawa H, Uno T, Barron JP: Comprehensive registry of esophageal cancer in Japan, 2002. Esophagus 2010;7:7–22.
7 Schlag PM: Randomized trial of preoperative chemotherapy for squamous cell carcinoma of the esophagus. The Chirurgische Arbeitsgemeinschaft für Onkologie der Deutschen Gesellschaft für Chirurgie Study Group. Arch Surg 1992;127:1446–1450.
8 Roth JA, Pass HI, Flanagan MM, Graeber GM, Rosenberg JC, Steinberg S: Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. J Thorac Cardiovasc Surg 1988;96:242–248.
9 Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, Estes N, Heller DG, Ajani J, Kocha W, Minsky BD, Roth JA: Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979–1984.
10 Law S, Fok M, Chow S, Chu KM, Wong J: Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg 1997;114: 210–217.
11 Ancona E, Roul A, Santi S, Merigliano S, Sileni VC, Koussis H, Zaninotto G, Bonavina L, Percchia A: Only pathologic complete response to neoadjuvant chemotherapy improve the long-term survival of patients with resectable squamous cell carcinoma. Cancer 2001;91:2165–2174.
12 Shimakawa T, Naritaka Y, Asaka S, Isohata N, Murayama M, Konno S, Yoshimatsu K, Shiozawa S, Katsube T, Ogawa K: Neoadjuvant chemotherapy (FAP) for esophageal cancer. Anticancer Res 2008;28:2321–2326.

13 Miyata H, Yoshioka A, Yamasaki M, Nushijima Y, Takiguchi S, Fujiwara Y, Nishida T, Mano M, Mori M, Doki Y: Tumor budding in tumor invasive front predicts prognosis and survival of patients with esophageal squamous cell carcinomas receiving neoadjuvant chemotherapy. Cancer 2009;115:3324–3334.
14 Ilzuka T, Kakegawa T, Ide H, Ando N, Watanabe H, Tanaka O, Takagi I, Isono K, Ishida K, Arimori M: Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal Oncology Group Trial. Jpn J Clin Oncol 1992;22:172–176.
15 Ilson DH, Ajani J, Bhalla K, Forastiere A, Huang Y, Patel P, Martin L, Donegan J, Pazdur R, Reed C, Kelsen DP: Phase II trial of paclitaxel, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 1998;16:1826–1834.
16 Ilson DH, Saltz L, Enzinger P, Huang Y, Komblith A, Gollub M, O'Reilly E, Schwartz G, DeGroff J, Gonzalez G, Kelsen DP: Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 1999;17:3270–3275.
17 Millar J, Scullin P, Morrison A, McClory B, Wall L, Cameron D, Philips H, Price A, Dunlop D, Eatock M: Phase II study of gemcitabine and cisplatin in locally advanced/metastatic oesophageal cancer. Br J Cancer 2005; 93:1112–1116.
18 Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24: 4991–4997.
19 Posner MR, Hershock DM, Blajman CR, Mickiewics E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Rarz LE, Cohen RB, Spaulding M, Tishler RB, Roth B, Viroglio R del C, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas AD, Norris CM Jr, Hadda RI, TAX 324 Study Group: Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357:1705–1715.
20 Park SR, Chun JH, Kim YW, Lee JH, Choi JS, Bae JM, Kim HK: Phase II study of low-dose docetaxel/fluorouracil/cisplatin in metastatic gastric cancer. Am J Clin Oncol 2005; 28:433–438.
21 Lorenzen S, Hentrich M, Haberl C, Heinemann V, Schuster T, Seronelt T, Roethling N, Peschel C, Lordick F: Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. Ann Oncol 2007;18:1673–1679.
22 Tebbutt N, Sourjina T, Strickland A, Van Hazel G, Ganju V, Gibbs D, Gebski V, Munro S, Cummins M: ATTX: Randomized phase II study evaluating weekly docetaxel-based chemotherapy combinations in advanced esophagogastric cancer, final results of an AGITG trial. J Clin Oncol 2007;25(suppl 18S):4528.
23 Ajani JA, Phan A, Ho L, Tetzlaff ED, Baker J, Wei Q: Phase I/II trial of docetaxel plus oxaliplatin and 5-fluorouracil (D-FOX) in patients with untreated advanced gastric or gastroesophageal cancer. J Clin Oncol 2007; 25(suppl 18S):4612.
24 Al-Batran SE, Hartmenn JT, Hofheinz R, Rethwisch V, Probst S, Stoehlmacher J, Clemens MR, Mahlberg R, Fritz M, Seipelt G, Sievert M, Pauligk C, Atmaca A, Jager E: Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008;19:1882–1887.
25 Overman MJ, Kazmi SM, Jhamb J, Lin E, Yao JC, Abbruzzese JL, Ho L, Ajani J, Phan A: Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. Cancer 2010;116:1446–1453.
26 Brücher BLDM, Weber W, Bauer M, Fink U, Avril N, Stein HJ, Werner M, Zimmerman F, Siewert JR, Schwaiger M: Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001;233:300–309.
27 Ott K, Weber WA, Lordick F, Becker K, Busch R, Herrmann K, Wieder H, Fink U, Schwaiger M, Siewert JR: Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol 2008;24:4692–4698.

Hindawi Publishing Corporation
Case Reports in Medicine
Volume 2010, Article ID 802312, 4 pages
doi:10.1155/2010/802312

Case Report

Successful Treatment of Cisplatin Overdose with Plasma Exchange

Yasuhiro Yamada,[1] Yoshiaki Ikuta,[2] Kisato Nosaka,[1] Nobutomo Miyanari,[2] Naoko Hayashi,[2] Hiroaki Mitsuya,[1] and Hideo Baba[2]

[1] *Department of Hematology & Infectious Diseases, Kumamoto University School of Medicine, Kumamoto 860-8556, Japan*
[2] *Department of Gastroenterological Surgery, Kumamoto University School of Medicine, Kumamoto 860-8556, Japan*

Correspondence should be addressed to Yasuhiro Yamada, yas-yas@sannet.ne.jp

Received 2 December 2009; Revised 27 January 2010; Accepted 27 January 2010

Academic Editor: Mohammad Abdollahi

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

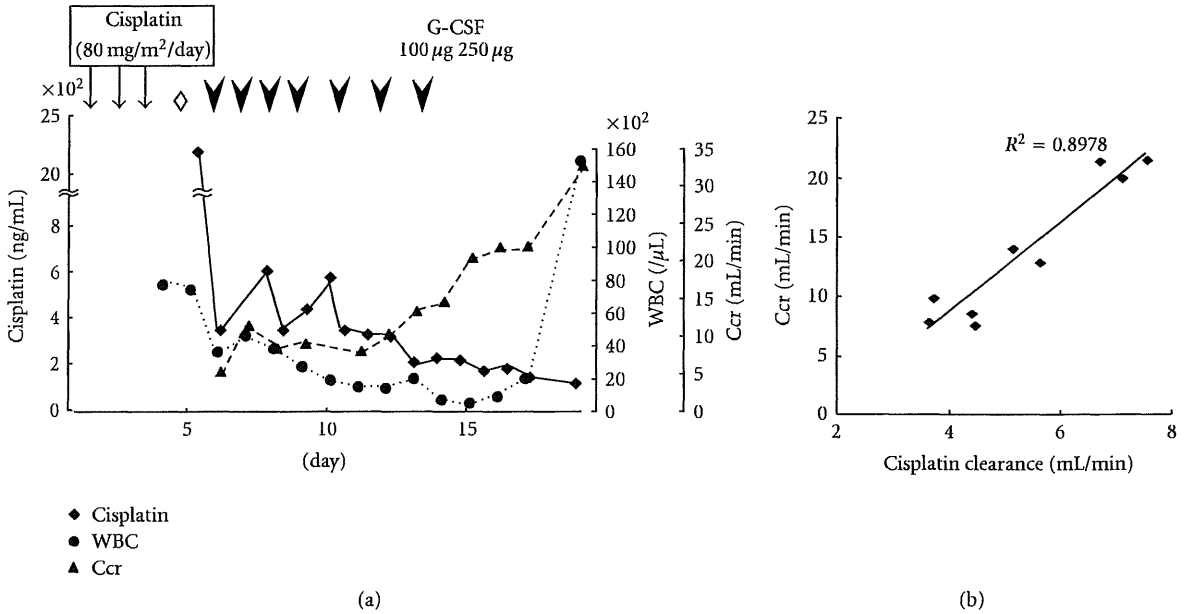

FIGURE 1: *Plasma cisplatin concentrations, leukocyte counts, Ccr values and platinum clearance values.* (a) An open diamond and arrow heads denote for dialysis and plasma exchange, respectively. (b) Note that cisplatin clearance approximately correlated with Ccr. WBC: white blood cell, G-CSF: granurocyte-colony-stimulating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

Acknowledgments

The authors would like to thank Nippon Kayaku co., Ltd., for assisting them in measuring platinum concentrations and the patient and his family for allowing them to report this article.

References

[1] T. H. Guthrie Jr. and L. Gynther, "Acute deafness. A complication of high-dose cisplatin," *Archives of Otolaryngology*, vol. 111, no. 5, pp. 344–345, 1985.

[2] J. L. Lagrange, E. Cassuto-Viguier, V. Barbe, et al., "Cytotoxic effects of long-term circulating ultrafiltrable platinum species and limited efficacy of haemodialysis in clearing them," *European Journal of Cancer*, vol. 30A, no. 14, pp. 2057–2060, 1994.

[3] J. H. Schiller, J. Rozental, K. D. Tutsch, and D. L. Trump, "Inadvertent administration of 480 mg/m^2 of cisplatin," *American Journal of Medicine*, vol. 86, no. 5, pp. 624–625, 1989.

[4] G. Chu, R. Mantin, Y. M. Shen, G. Baskett, and H. Sussman, "Massive cisplatin overdose by accidental substitution for carboplatin. Toxicity and management," *Cancer*, vol. 72, no. 12, pp. 3707–3714, 1993.

[5] H. K. Jung, J. Lee, and S. N. Lee, "A case of massive cisplatin overdose managed by plasmapheresis," *The Korean Journal of Internal Medicine*, vol. 10, no. 2, pp. 150–154, 1995.

[6] J. H. Choi, J. C. Oh, K. H. Kim, S. Y. Chong, M. S. Kang, and D. Y. Oh, "Successful treatment of cisplatin overdose with plasma exchange," *Yonsei Medical Journal*, vol. 43, no. 1, pp. 128–132, 2002.

[7] B. Erdlenbruch, A. Pekrun, H. Schiffmann, O. Witt, and M. Lakomek, "Topical topic: accidental cisplatin overdose in a child: reversal of acute renal failure with sodium thiosulfate," *Medical and Pediatric Oncology*, vol. 38, no. 5, pp. 349–352, 2002.

[8] G. Hofmann, T. Bauernhofer, P. Krippl, et al., "Plasmapheresis reverses all side-effects of a cisplatin overdose–a case report and treatment recommendation," *BMC Cancer*, vol. 6, article 1, 2006.

[9] D. Sheikh-Hamad, K. Timmins, and Z. Jalali, "Cisplatin-induced renal toxicity: possible reversal by N-acetylcysteine treatment," *Journal of the American Society of Nephrology*, vol. 8, no. 10, pp. 1640–1644, 1997.

[10] J. J. Offerman, S. Meijer, D. T. Sleijfer, et al., "Acute effects of cis-diamminedichloroplatinum (CDDP) on renal function," *Cancer Chemotherapy and Pharmacology*, vol. 12, no. 1, pp. 36–38, 1984.

[11] C. Charlier, P. Kintz, N. Dubois, and G. Plomteux, "Fatal overdose with cisplatin," *Journal of Analytical Toxicology*, vol. 28, no. 2, pp. 138–140, 2004.

[12] D. Appenroth and K. Winnefeld, "Role of glutathione for cisplatin nephrotoxicity in young and adult rats," *Renal Failure*, vol. 15, no. 2, pp. 135–139, 1993.

[13] K. Takada, T. Kawamura, M. Inai, et al., "Pharmacokinetics of cisplatin in analbuminemic rats," *Biopharmaceutics and Drug Disposition*, vol. 20, no. 9, pp. 421–428, 1999.

[14] F. Brivet, J. M. Pavlovitch, A. Gouyette, M. L. Cerrina, G. Tchernia, and J. Dormont, "Inefficiency of early prophylactic hemodialysis in cis-platinum overdose," *Cancer Chemotherapy and Pharmacology*, vol. 18, no. 2, pp. 183–184, 1986.

[15] I. M. Pike and M. H. Arbus, "Cisplatin overdosage," *Journal of Clinical Oncology*, vol. 10, no. 9, pp. 1503–1504, 1992.

[16] J. T. Hartmann and H. P. Lipp, "Toxicity of platinum compounds," *Expert Opinion on Pharmacotherapy*, vol. 4, no. 6, pp. 889–901, 2003.

[17] A. Bai, H. Kojima, M. Hori, et al., "Priming with G-CSF effectively enhances low-dose Ara-C-induced in vivo apoptosis in myeloid leukemia cells," *Experimental Hematology*, vol. 27, no. 2, pp. 259–265, 1999.

[18] C. F. Perno, R. Yarchoan, D. A. Cooney, et al., "Replication of human immunodeficiency virus in monocytes. Granulocyte/macrophage colony-stimulating factor (GM-CSF) potentiates viral production yet enhances the antiviral effect mediated by 3′-azido-2′3′-dideoxythymidine (AZT) and other dideoxynucleoside congeners of thymidine," *Journal of Experimental Medicine*, vol. 169, no. 3, pp. 933–951, 1989.

Surg Today (2012) 42:29–34
DOI 10.1007/s00595-011-0016-5

ORIGINAL ARTICLE

The central vein access port and catheter in outpatient chemotherapy for colorectal cancer: a retrospective study of 101 patients

Hiroshi Sawayama · Naoko Hayashi · Masayuki Watanabe · Hiroshi Takamori · Toru Beppu · Hideo Baba

Received: 15 April 2010 / Accepted: 29 July 2010 / Published online: 22 November 2011

Abstract
Purpose The central venous access port (CV-port) system was examined in a series of colorectal cancer (CRC) patients.
Methods One hundred and one CRC patients underwent chemotherapy with the 5-fluorouracil + oxaliplatin (FOLFOX) or 5-fluorouracil + irinotecan regimen. The complications of the CV-port system were retrospectively assessed.
Results The CV-port system was placed in a total of 101 patients. The patients received a total of 1035 courses of these regimens. Eight complications occurred in the 101 patients (7.9%). The complications included three instances of catheter rupture, two thrombotic events around the catheter, and three infections at the site of the port or catheter. The complications were identified after a median of nine courses (range 6–16) and 135 days after the placement of the CV-port system. Sixty-six of the 101 patients switched their regimen from FOLFOX to another regimen, and 4 of these 66 patients (6.1%) experienced complications associated with the CV-port system. There were 25 subjects who were admitted to the hospital emergency wing during the chemotherapeutic regimens, and 4 of these patients (16%) had complications associated with the CV-port system.
Conclusions The complications of the CV-port system occurred at a defined rate, therefore the early diagnosis and the appropriate treatment to address these complications is crucial.

Keywords Colorectal cancer · Outpatient chemotherapy · Central venous access port · Complication · Pinch-off

Introduction

Completely implantable port systems were first introduced in the early 1980s. A variety of anticancer agents have been administered while using the devices without difficulty, and the patient acceptance of this system is excellent [1]. Late complications may occur, including catheter rupture and embolization, venous thrombosis, pocket infection, and port-related bacteremia. However, these devices have a long working life and a low rate of patient complications, and are of great value to patients who require long-term or cyclic intravenous treatments [2]. These data support the increasing use in current oncologic medical practices. The gastrointestinal division originally used the central venous access port (CV-port) system, either for administering chemotherapy to patients with gastric cancer, to provide nourishment to patients with short bowel syndrome, or for the treatment of patients with other conditions. The CV-port system has been extensively used since its introduction in colorectal cancer (CRC) patients receiving the 5-fluorouracil + oxaliplatin (FOLFOX) or 5-fluorouracil + irinotecan (FOLFIRI) + bevacizumab [3] chemotherapy.

A summary of this study was presented at the 108th Annual Meeting of the Japan Surgical Society in 2008 and the 46th Annual Meeting of the Japan Society of Clinical Oncology in 2008.

H. Sawayama · N. Hayashi · M. Watanabe · H. Takamori · T. Beppu · H. Baba (✉)
Department of Gastroenterological Surgery,
Graduate School of Medical Sciences,
Kumamoto University, 1-1-1 Honjo,
Kumamoto 860-8556, Japan
e-mail: hdobaba@kumamoto-u.ac.jp

Patients and methods

Patients and chemotherapeutic regimens

One hundred and three CRC patients underwent FOLFOX or FOLFIRI chemotherapy between April 2005 and March 2008 at our institution. One hundred and one of the 103 patients (98%) underwent CV-port system placement. Two patients could not receive the CV-port, because one patient had a mechanical valve and the other experienced difficulty in the placement of the CV-port. The 101 remaining patients (range 27–82 years of age, with a median age of 62 years) underwent chemotherapy for unresectable metastatic CRC, and also underwent adjuvant chemotherapy following hepatectomy. The regimens consisted of the modified FOLFOX-6 (m-FOLFOX 6), FOLFOX-4, or FOLFIRI regimens. The regimens consisted of a continuous infusion of 5-fluorouracil (5-FU) using a portable disposable pump, which was manufactured by Baxter (Deerfield, IL, USA).

Ports and routes of access to the central vein and maintenance of ports

Central venous access ports were placed by surgeons in the CRC patients. An indwelling catheter was inserted from the right subclavian vein at the lateral side using diagnostic imaging guidance and fluoroscopy to confirm that the catheter was placed in the superior vena cava. The ports were placed at the jugular vein or the inguinal vein if the surgeon experienced difficulty placing it in the subclavian vein. All 101 patients had a single-lumen Groshong 8-F catheter and an MRI-Port (CR Bard, Summit, NJ, USA) implanted. The first one or two courses of the regimen were administered while the patients were hospitalized in order to monitor any adverse events. The CV-port was put in place, and the patients were educated about the chemotherapy. After one or two courses of chemotherapy in the hospital, the patients underwent chemotherapy every 2 weeks as outpatients. Their ports were punctured by a doctor with a Huber-pointed needle. The doctor confirmed whether there was redness, swelling, or pain around the port, and confirmed that the natural drip was smooth before the patient was connected to the pump. The state of the catheter was regularly checked with chest X-rays every 3 months. The needle was removed without a saline flush after chemotherapy by the patients themselves or their family doctor.

The frequency and types of complications involving CV-ports and catheters were retrospectively evaluated. We also examined the instances of emergency hospital outpatient admission during chemotherapy and the reasons for changing to other regimens. The purpose of the present study was to demonstrate the placement methods and maintenance of the CV-port system for preventing and identifying late complications.

Results

A total of 101 patients underwent the FOLFOX regimen, and a total of 750 courses were administered (median 8 courses per patient). Forty of the 101 patients also received the FOLFIRI regimen, and a total of 270 courses were administered (median 6 courses). An overall total of 1035 courses were administered (median 10). Eight patients had central vein access port and catheter complications (7.9%). The complications associated with the central vain access port and catheter occurred at a median of 9 courses (range 6–16) and at a median time of 135 days after putting the CV-port system in place (Table 1).

Table 1 Complications of the central venous access port and catheter

	Total patients	Patients with complications
Number of patients	101	8
Sex, male/female	66/35	6/2
Age, median (range)	62 (27–82)	69 (65–81)
Courses of chemotherapy, median (range)	10 (1–25)	9 (6–16)

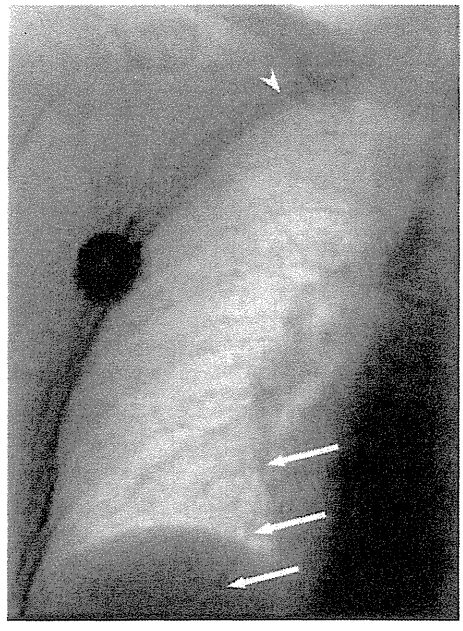

Fig. 1 Pinch-off syndrome and fracture of the catheter. The catheter was transected between the clavicle and the first rib (*arrowhead*), and the tip of the catheter was wedged into the pulmonary artery (*arrow*)

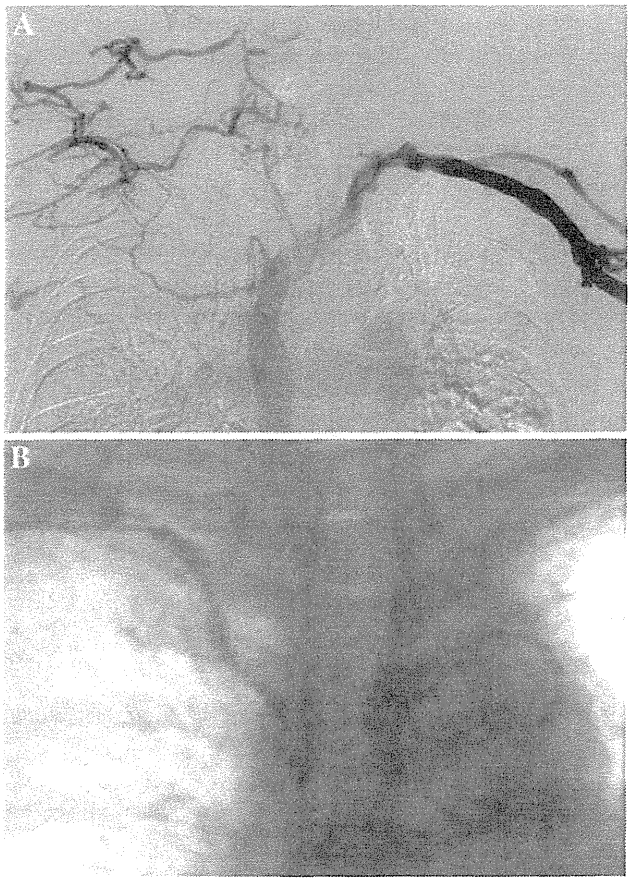

Fig. 2 A case of thrombosis around the site of the catheter (fibrin-sheath formation). **a** Contrast medium was injected from the bilateral median veins; however, the contrasting effect was not seen in the right subclavian vein, and it was concluded that a collateral pathway had developed. **b** There was no outflow of contrast media from the catheter tip, and a light contrasting effect was observed around the catheter

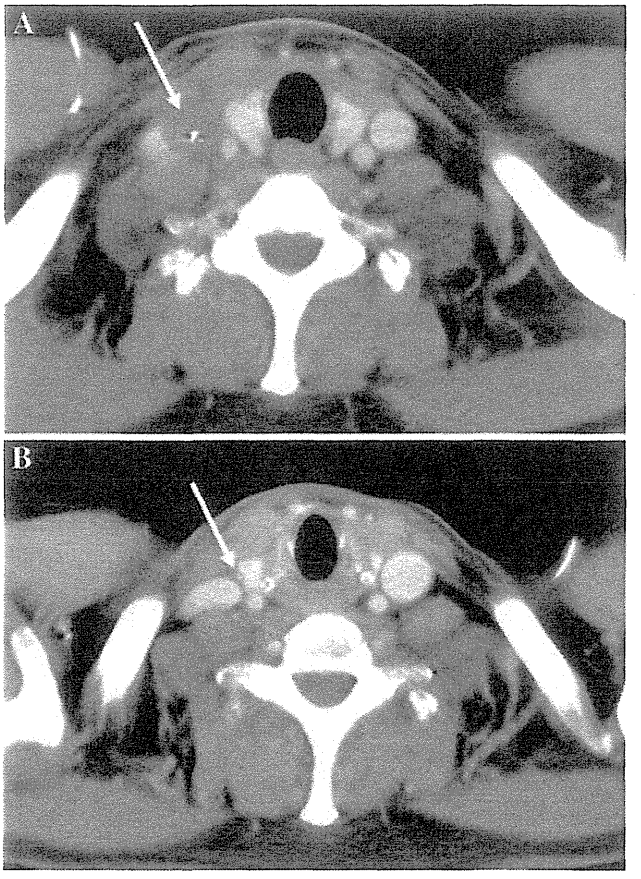

Fig. 3 Cases of thrombosis in the internal jugular vein. **a** The tip of the catheter was detected in an internal jugular vein and there was thrombosis around the catheter (*arrow*), as observed on contrast computed tomography. **b** Thrombosis in the internal jugular vein improved (*arrow*) after 5 months of warfarin treatment

The incidents involved catheter pinch-off syndrome (POS) and fracture of the catheter ($n = 1$, Fig. 1), thrombosis around the catheter ($n = 2$, Figs. 2, 3), the connection portion of the port and catheter coming off ($n = 1$, Fig. 4), the flexure of the catheter ($n = 1$, Fig. 5), and the infection of the site of the port or catheter ($n = 3$) (Table 2).

Sixty-six of the 101 patients changed their regimen from FOLFOX to other regimens. Thirty-seven subjects were switched because of progressive disease (56.1%), 22 patients switched due to an adverse event (33.3%), and 4 patients were switched because of complications associated with the CV-port system (6.1%). The adverse events included peripheral neuropathy in 13 patients (19.7%), allergy in 5 patients (7.6%), and myelosuppression, interstitial pneumonia, and one patient's request (Table 3).

There were 25 patients admitted to the emergency department during the FOLFOX or FOLFIRI chemotherapeutic

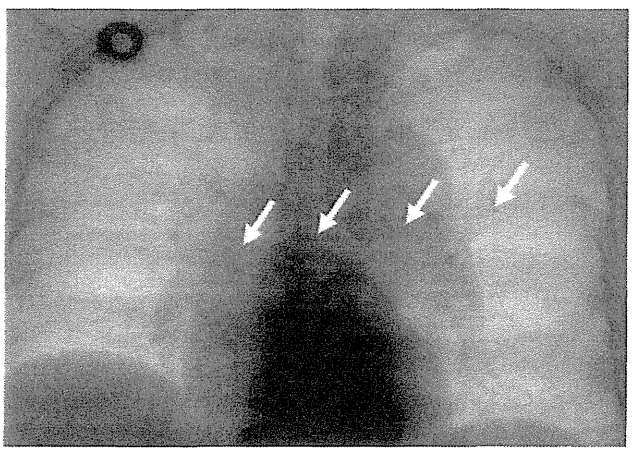

Fig. 4 Port connector rupture, connection portion coming off. The catheter was wedged into the pulmonary artery (*arrow*). The catheter was not fractured, and the rupture was judged to be caused by the catheter separating from the port connector

regimen, and 3 of 25 patients (12.5%) had adverse effects including pyrexia with neutropenia, severe anorexia, and acute exacerbation of interstitial pneumonia. However,

4 subjects (16.7%) required an emergency hospital admission due to complications associated with the CV-port system (Table 4).

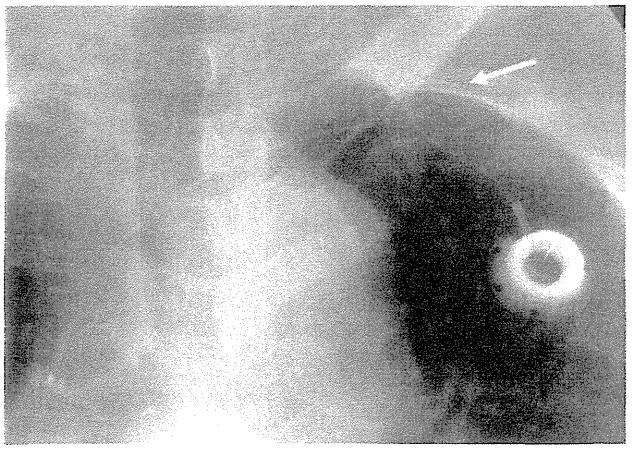

Fig. 5 Flexure and obstruction of the catheter. The catheter was bent in the subcutis (*arrow*), not in the subclavian vein, and was therefore manually repositioned

Discussion

FOLFOX or FOLFIRI regimen administration with a continuous infusion of 5-FU may be switched to a combination of an oral anticancer drug, such as S-1 or capecitabine, with irinotecan or oxaliplatin (IRIS, XELOX, etc.) [4–6]. However, the FOLFOX and FOLFIRI regimens are administered to CRC patients because there is a large amount of evidence indicating the efficacy, safety, and feasibility of these regimens.

Complications have been associated with the long-term placement of a CV-port and catheter [7–10]. The current series demonstrated complications in 8 of 101 patients (7.9%). The frequency of complications that occurred in association with the CV-port system during the chemotherapeutic treatment of outpatients in the present study was consistent with past reports. Several CRC patients required hospitalization for complications associated with the catheter. Furthermore, the complications of the CV-port and catheter caused some patients to change to another regimen (6.1%) or to require emergency treatment (16.7%). Outpatient chemotherapy was safely performed for the

Table 2 Summary of complications of central venous access-ports or catheters, excluding three patients with a catheter infection

Age (years)/sex	Chief complaint	Complication	Treatment
71/F (9)[a]	Pain around the port	Pinch off syndrome	Extraction of the catheter by interventional radiology
		Fracture of the catheter	Change to IRIS regimen
68/M (5)	Pain around the port	Thrombosis	Extraction of the catheter
		Fibrin sheath formation	Change to IRIS regimen
62/M (9)	Right neck pain	Thrombosis, dislocation	Extraction of the catheter
		Right internal jugular vein	Anticoagulant and change to the IRIS regimen
73/M (11)	Swelling around port	Port connector rupture	Extraction of the catheter by interventional radiology
		Connection portion coming off	Catheter replacement
81/M (13)	Poor infusion	Flexure of the catheter	Repositioning: stretch the catheter out
		Bent in subcutis	

IRIS regimen: combination therapy of S-1 and irinotecan

[a] Courses of chemotherapy in parentheses

Table 3 Reasons for changing from the FOLFOX regimen to another regimen

Reason (n = 66)	Number	Percentage	Age (years) Median	Sex M/F	Courses of chemotherapy
Progressive disease	37	56.1	61	24/13	8
Adverse events	22	33.3			
Peripheral neuropathy	13	19.7	63	10/3	10
Allergy	5	7.6	55	2/3	10
Myelosuppression	2	3.0	58	2/1	4
Interstitial pneumonia	1	1.5	75	1/0	8
Patient's request	1	1.5	44	0/1	2
Complication of CV-port system	4	6.1	69	3/1	12
Others	3	4.5	61	2/1	10

FOLFOX 5-fluorouracil + oxaliplatin, *CV-port* central venous access port

Table 4 Emergency hospital admissions during FOLFOX or FOLFIRI chemotherapy

Reason ($n = 25$)	Number	Percentage
Progressive disease	9	36
Adverse events	3	12
Peripheral neuropathy	0	0
Allergy	0	0
Myelosuppression	0	0
Interstitial pneumonia	1	4
Pyrexia with the neutropenia	1	4
Severe anorexia	1	4
Complication of CV-port system	4	16
Surgical site infection	2	8
Others	7	28

FOLFOX 5-fluorouracil + oxaliplatin, *FOLFIRI* 5-fluorouracil + irinotecan, *CV-port* central venous access port

majority of cases in our hospital. However, some issues remained, such as the occurrence of complications associated with the CV-port system, which led to changes to either another treatment regimen or to emergency hospital admission. These complications associated with the port and catheter included three instances of catheter rupture and embolization, venous thrombosis, and infection. We herein discuss the placement methods, the appropriate maintenance of CV-ports, and the measures taken to address these complications when they occur.

Catheter rupture and embolization

Pinch-off syndrome occurs when the CV access devices placed via the subclavian vein become obstructed due to thrombosis, impingement against a vein wall, or compression between the clavicle and the first rib. Luminal narrowing and complete catheter fracture occur in approximately 1% of catheter placements [11]. One case of catheter pinch-off was experienced at our institution during the study period. The patient did not report an active exercise history, but the subject had a small physique, weighed 45 kg, and was 145 cm in height. A catheter tip measuring 5 cm in length caused an embolus to a pulmonary artery. The catheter was withdrawn with a snare from the right inguinal vein by a radiologist. A puncture point is important to avoid pinch-off points. The catheter should be preferentially placed on the lateral side of the subclavian vein or in the internal jugular vein to avoid a pinch-off point [12]. Peripheral arm ports have been implanted in some CRC patients with no incidences of catheter POS [13]. The supraclavicular technique provides the best results with regard to the percutaneous introduction of large-bore central venous catheters [14]. At our institution, the most general approach from the right subclavian vein is the first choice of a puncture. There are no reports of cases that have an increased tendency to have pinch-offs, but we perform a puncture from another portion; namely, the right supraclavian vein or left subclavian vein, not the right subclavian vein, due to the fact that patients who actively exercise or have a small physique may experience POS.

Port connector rupture is usually caused by the method used to place the CV-port device. The method for connecting a port and catheter varies with the CV-port device, and the surgeon must confirm the type of CV-port device and the method used to ensure a proper connection.

Venous thrombosis

Catheter-related central venous thrombosis (CRCVT) occurs at a rate of 12–66% [15, 16]. In a prospective study, CRCVT was observed in 63 of 95 (66%) patients; however, it was symptomatic in only 4 of 63 (6%) of these patients [15]. There is no prognostic marker for venous thrombotic complications [16]. Three recent clinical trials investigated the effects of prophylactic anticoagulation with either low molecular weight heparin or low dose warfarin in cancer patients who had central venous devices [17–19]. However, these studies did not support the routine use of prophylactic anticoagulation in cancer patients with venous catheters to prevent catheter-induced thrombosis. Based on these results, routine anticoagulation is not recommended [20]. Anticoagulant administration just after the placement of the CV-port system is not used in our hospital. Two thrombosis cases were detected at our institution during the study period. These patients were diagnosed by injecting contrast media from the port and median vein on the port insertion side. The IRIS regimen (a combination therapy of the oral anticancer drug S-1 and irinotecan) was administered for the current patient series when the CV-port could not be replaced due to thrombosis. In the present study, thrombosis improved after the administration of anticoagulant therapy. Both patients had the CV-port system put in place again, and the FOLFOX regimen was restarted.

Infection

A diagnosis of a catheter-related infection might be difficult in the absence of local signs of inflammation [21]. Routine device removal is not recommended for most patients. Empirical antibiotics are administered when the patient presents with sepsis or septic shock. Port systems must be removed in case of a persistent relapse of infection after antibiotic treatment, at signs of port or catheter tunnel infection, for unstable patients, or after the development of systemic complications [22, 23]. However, CRC patients undergoing perioperative chemotherapy have had highly

invasive surgery, and the general opinion is that these guidelines do not apply to most of these patients. A high fever after CRC resection is usually attributable to an infection at the surgical site or an infection of the CV-port system. In our hospital we experienced a patient who demonstrated complications associated with a biliary fistula after hepatectomy, who continued to have a high fever after antibiotic treatment. The CV-port system was withdrawn, but no bacteria were detected on the catheter. However, we thought that the CV-port system should be withdrawn in such a case, contrary to popular opinion.

In conclusion, the management of the CV-port system is an important factor in the administration of chemotherapy to outpatients with CRC. We have described proper CV-port system placement and have summarized a recent report about the tendencies of port complications. We have also explained measures that were used to treat the complications in our experimental cases. The chemotherapeutic treatment of outpatients with the CV-port system is therefore best performed when the physicians are aware of these complications and how to best treat patients for CV-port complications without compromising their anticancer treatment.

References

1. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery. 1982;92:706–12.
2. Torramade JR, Cienfuegos JA, Hernandez JL, Pardo F, Benito C, Gonzalez J, et al. The complications of central venous access systems: a study of 218 patients. Eur J Surg. 1993;159:323–7.
3. Konno H, Yamamoto M, Ohta M. Recent concepts of antiangiogenic therapy. Surg Today. 2010;40:494–500.
4. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008;26:2006–12.
5. Tsunoda A, Yasuda N, Nakao K, Narita K, Watanabe M, Matsui N, et al. Phase II study of S-1 combined with irinotecan (CPT-11) in patients with advanced colorectal cancer. Oncology. 2009;77:192–6.
6. Ishida H, Miyake Y, Fukunaga M, Watanabe Y, Kato T, Takemoto H, et al. A feasibility study of UFT/LV and irinotecan (TEGAFIRI) in advanced or metastatic colorectal cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) PROG 0304. Jpn J Clin Oncol. 2009;39:601–5.
7. Biffi R, de Braud F, Orsi F, Pozzi S, Mauri S, Goldhirsch A, et al. Totally implantable central venous access ports for long-term chemotherapy. A prospective study analyzing complications and costs of 333 devices with a minimum follow-up of 180 days. Ann Oncol. 1998;9:767–73.
8. Charvat J, Linke Z, Horaekova M, Prausova J. Implantation of central venous ports with catheter insertion via the right internal jugular vein in oncology patients: single center experience. Support Care Cancer. 2006;14:1162–5.
9. Yip D, Funaki B. Subcutaneous chest ports via the internal jugular vein. A retrospective study of 117 oncology patients. Acta Radiol. 2002;43:371–5.
10. Funaki B, Szymski GX, Hackworth CA, Rosenblum JD, Burke R, Chang T, et al. Radiologic placement of subcutaneous infusion chest ports for long-term central venous access. AJR Am J Roentgenol. 1997;169:1431–4.
11. Hinke DH, Zandt-Stastny DA, Goodman LR, Quebbeman EJ, Krzywda EA, Andris DA. Pinch-off syndrome: a complication of implantable subclavian venous access devices. Radiology. 1990;177:353–6.
12. Andris DA, Krzywda EA, Schulte W, Ausman R, Quebbeman EJ. Pinch-off syndrome: a rare etiology for central venous catheter occlusion. JPEN J Parenter Enter Nutr. 1994;18:531–3.
13. Kawamura J, Nagayama S, Nomura A, Itami A, Okabe H, Sato S, et al. Long-term outcomes of peripheral arm ports implanted in patients with colorectal cancer. Int J Clin Oncol. 2008;13:349–54.
14. Fazeny-Dorner B, Wenzel C, Berzlanovich A, Sunder-Plassmann G, Greinix H, Marosi C, et al. Central venous catheter pinch-off and fracture: recognition, prevention and management. Bone Marrow Transplant. 2003;31:927–30.
15. De Cicco M, Matovic M, Balestreri L, Panarello G, Fantin D, Morassut S, et al. Central venous thrombosis: an early and frequent complication in cancer patients bearing long-term silastic catheter. A prospective study. Thromb Res. 1997;86:101–13.
16. Cortelezzi A, Moia M, Falanga A, Pogliani EM, Agnelli G, Bonizzoni E, et al. Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: a prospective multicentre study. Br J Haematol. 2005;129:811–7.
17. Verso M, Agnelli G, Bertoglio S, Di Somma FC, Paoletti F, Ageno W, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. J Clin Oncol. 2005;23:4057–62.
18. Couban S, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol. 2005;23:4063–9.
19. Karthaus M, Kretzschmar A, Kroning H, Biakhov M, Irwin D, Marschner N, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol. 2006;17:289–96.
20. Vescia S, Baumgartner AK, Jacobs VR, Kiechle-Bahat M, Rody A, Loibl S, et al. Management of venous port systems in oncology: a review of current evidence. Ann Oncol. 2008;19:9–15.
21. Bouza E, Burillo A, Munoz P. Catheter-related infections: diagnosis and intravascular treatment. Clin Microbiol Infect. 2002;8:265–74.
22. Ouriel K. Preventing complications of central venous catheterization. N Engl J Med. 2003;348:2684–6 (author reply 2684–6).
23. Kovacevich DS, Papke LF. Guidelines for the prevention of intravascular catheter-related infections: Centers for Disease Control and Prevention. Nutr Clin Pract. 2003;18:95–6.

Gastric Cancer
DOI 10.1007/s10120-011-0124-3

ORIGINAL ARTICLE

A randomized phase-II trial comparing sequential and concurrent paclitaxel with oral or parenteral fluorinated pyrimidines for advanced or metastatic gastric cancer

Kazuhiro Nishikawa · Satoshi Morita · Takanori Matsui · Michiya Kobayashi · Yoji Takeuchi · Ikuo Takahashi · Seiji Sato · Yumi Miyashita · Akira Tsuburaya · Junichi Sakamoto · Yoshihiro Kakeji · Hideo Baba

Received: 27 July 2011 / Accepted: 26 November 2011

Abstract

Background The purpose of this study was twofold: (1) to compare S-1 with infusional 5-fluorouracil (FU) to determine which would be a better partner of paclitaxel (PTX), and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.

Methods The 161 eligible patients were randomized into four arms to receive the following regimens: A (sequential), intravenous 5-FU at 800 mg/m^2 for 5 days every 4 weeks followed by weekly PTX at 80 mg/m^2; B (sequential), S-1 at 80 mg/m^2 for 4 weeks and 2-week rest followed by PTX; C (concurrent), intravenous 5-FU at 600 mg/m^2 for 5 days and weekly PTX at 80 mg/m^2 every 4 weeks; and D (concurrent), S-1 for 14 days and PTX at 50 mg/m^2 on days 1 and 8 every 3 weeks. The primary endpoint was the overall survival (OS) rate at 10 months.

Results The ten-month OS rates in arms A, B, C, and D were 63, 65, 61, and 73%, respectively. The OS was best in the concurrent S-1/PTX arm, with a mean survival time of

K. Nishikawa (✉)
Department of Surgery, Osaka General Medical Center, 3-1-56 Bandai-higashi, Sumiyoshi-ku, Osaka 558-8558, Japan
e-mail: kazuno1@gh.opho.jp

S. Morita
Department of Biostatistics and Epidemiology, Yokohama City University, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan

T. Matsui
Department of Gastroenterological Surgery, Aichi Cancer Center, Aichi Hospital, 18 Kuriyado, Kakemachi, Okazaki 444-0011, Japan

M. Kobayashi
Department of Human Health and Medical Sciences, Kochi Medical School, Kohasu-Okocho, Nankoku, Kochi 783-8505, Japan

Y. Takeuchi
Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan

I. Takahashi
Department of Surgery, Matsuyama Red Cross Hospital, 1 Bunkyomachi, Matsuyama, Ehime 790-8524, Japan

S. Sato
Department of Surgery, Saga Prefectural Hospital Koseikan, 1-12-9 Mizugae, Saga 840-8571, Japan

Y. Miyashita
Epidemiological and Clinical Research Information Network, 21-7 Shogoin, Sanno-cho, Sakyo-ku, Kyoto 606-8392, Japan

A. Tsuburaya
Department of Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0851, Japan

J. Sakamoto
Department of Young Leaders' Program in Health Care Administration, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Y. Kakeji
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

H. Baba
Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan

Published online: 26 January 2012

15.4 months, but no significant difference was observed between the four arms. Response rates were higher in the concurrent arms than in the sequential arms.

Conclusion Our study did not show sufficient prolongation of survival with the concurrent strategy to proceed to a phase-III trial; however, the sequential arms showed survival comparable to that in the concurrent arms, with less toxicity. In patients who are ineligible for cisplatin (CDDP), sequential treatment starting with S-1 and proceeding to PTX would be a good alternative strategy, considering quality of life (QOL) and the cost-benefits of an oral agent as first-line treatment.

Keywords Advanced gastric cancer · Paclitaxel · S-1 · Sequential chemotherapy · Concurrent combination chemotherapy · Randomized phase-II trial

Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide [1]. Most patients (except those from northeast Asian countries) present with advanced, inoperable, or metastatic disease, and the 5-year survival rate is approximately 10–15%. Palliative chemotherapy for advanced disease improves survival as compared with the best supportive care [2–4]. Despite the innumerable efforts of investigators in various countries to test various chemotherapeutic and immunotherapeutic agents and combination regimens, there has been little progress in the therapy for patients with advanced gastric cancer.

Probably because there is less evidence regarding the treatment of gastric cancer compared to that of other malignancies, the standard treatment for gastric cancer differs from country to country, although most of the "standard" regimens do not have sufficient evidence. Moreover, the insurance systems in most western countries approve only first-line treatment, and in these countries, doublet or triplet therapies could be the standard choice, while some countries, including Japan, approve second- and greater-line strategies, where we can choose not only concurrent but also sequential strategies. Reflecting these historical and social circumstances, "standard" treatment for gastric cancer shows wide variety, with some confusion. In Japan, the evidence-based standard regimen involved continuous infusion of 5-fluorouracil (5-FU) only (JCOG9205) before the results of the Japan Clinical Oncology Group (JCOG) 9912 and SPIRITS trials had been obtained [5–7]. After the results of SPIRITS trial were shown, S-1 plus cisplatin (CDDP) has been accepted as the standard first-line treatment for patients with good condition, but S-1 without CDDP was also widely used in general practice. This means we still need an alternative strategy, whose sequence starts from a fluoropyrimidine (infusional 5-FU or oral S-1) with or without other agents.

As for candidates as the fluoropyrimidine partner, some potent agents have been approved for gastric cancer in the past two decades. One of the promising agents was paclitaxel (PTX) [8], which had shown beneficial results in single use or concurrent use with a fluoropyrimidine [9–12]. However, these studies were conducted as single-arm phase I–II trials. Hence, the choice between sequential and concurrent strategies for fluoropyrimidine and PTX remains unclear.

We therefore planned a randomized phase-II trial to compare the following four treatment regimens: A, sequential 5-FU monotherapy followed by PTX monotherapy; B, sequential S-1 monotherapy followed by PTX monotherapy; C, concurrent 5-FU plus PTX [11]; and D, concurrent S-1 plus PTX [12]. The purpose of the study was twofold: (1) to compare S-1 with infusional 5-FU to determine which was the better partner of PTX, and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.

Patients and methods

The detailed study design and protocol treatment of this study has already been described by Morita et al. [13]. Below we outline a summary of the methodological issues in this study with the protocol (informed consent form) that was amended after the SPIRITS trial.

Eligibility criteria

Patients more than 20 years of age with histologically confirmed non-resectable advanced or recurrent gastric cancer were eligible. Patients who had undergone prior anti-tumor therapy (except for surgery and postoperative adjuvant chemotherapy) were excluded. Patients had to have adequate renal, hepatic, hematologic, and cardiac function, with an Eastern Cooperative Oncology Group performance status (PS) of 0–1. Patients had to be able to take food via the oral route to be considered for enrolment in the study.

The protocol was approved by the Institutional Review Board (IRB) of each institution, and written informed consent was obtained before treatment. Participating investigators were instructed to send an eligibility criteria report to the data center operated by the non-profit organization Epidemiological and Clinical Research Information Network (ECRIN). Eligible patients were registered and then randomized to receive either of the four treatment regimens (A, B, C, and D), using a centralized dynamic

randomization method with the following balancing factors: measurable disease according to criteria set by Response Evaluation Criteria in Solid Tumours (yes/no); disease type [inoperable advanced/postoperative recurrent (with postoperative chemotherapy)/postoperative recurrent (with no postoperative chemotherapy)]; PS (0/1); peritoneal metastasis based on diagnosis with images (yes/no); age (<75 years/≥75 years), and institution. Information regarding the necessary follow-up examinations and chemotherapy schedule was then sent from the ECRIN data center. The accrual started in December 2005 and was continued for 3 years.

Projected treatments

Based on previous trials, we adapted four promising regimens for this selection design trial [13]. Patients in arm A received sequential therapy with intravenous (i.v.) 800 mg/m^2 5-FU daily for 5 days every 4 weeks until progression, followed by PTX 80 mg/m^2 on days 1, 8, and 15 every 4 weeks. Patients in arm B received sequential therapy with 80 mg/m^2 of oral S-1 daily for 4 weeks and 2-week rest after the administration (total of 6 weeks per single course) until progression. This was followed by PTX, utilizing the same administration dose and schedule as that in arm A's second-line PTX. Patients in arm C received a combination therapy with 600 mg/m^2 5-FU (i.v.) daily for 5 days from day 1 and infusion of 80 mg/m^2 PTX on days 8, 15, and 22 every 4 weeks. Patients in arm D received a combination therapy with 80 mg/m^2 oral S-1 for 14 days from day 1 and infusion of 50 mg/m^2 PTX on days 1 and 8 every 3 weeks. In the sequential treatment arms A and B, the administration of 5-FU or S-1 monotherapy was discontinued if the following were observed: (1) disease progression or occurrence of new disease; (2) grade-4 nonhematological toxicities evaluated according to the Common Terminology Criteria for Adverse Events version 3.0; (3) adverse events causing patients to refuse treatment or causing a clinician to discontinue treatment; (4) increase in the tumor markers carcinoembryonic antigen (CEA) and/or cancer antigen (CA) 19-9 in two or more consecutive measurements or symptomatic progression (e.g., cancer pain and dysphagia). An irinotecan-containing regimen was recommended for use in case further lines of treatment were to be given.

Follow-up

Disease progression and occurrence of new disease were examined using radiographs, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, and thoracic CT and measurements of the tumor markers CEA and CA19-9. These examinations were performed at baseline and at least every 4–5 weeks during treatment. Blood tests and symptom checks were performed before treatment and at least every 2 weeks during treatment. In cases where therapy was discontinued owing to toxicity, clinicians followed up patients until they recovered from the effects of toxicity.

Study design and statistical methods

The primary aim of this study was to compare treatment regimens A–D in terms of the primary endpoint of the 10-month overall survival (OS) rate. In addition, OS and treatment failure curves were constructed as time-to-event plots using the Kaplan–Meier method [14]. Time-to-event curves were compared using log-rank tests and the hazard ratio (HR) estimated by Cox regression models [15]. The prevalence of grade-3 or grade-4 adverse events was compared between the treatment arms. Calculation of the sample size required 40 patients in each arm to assure 80% probability in order to select the best treatment arm [16] as long as the true expected 10-month OS rate exceeded that of any other arm by at least 15%. The total number of patients to be accrued was set at 160.

Protocol amendment after SPIRITS trial

After the results of the SPIRITS trial were publicized, standard first-line therapy in Japan shifted from monotherapies with 5-FU or S-1 to an S-1/CDDP combination. The protocol committee of the present trial discussed this issue and decided not to change the protocol treatments, because none of the treatment arms has actually been shown to be inferior to the S-1/CDDP combination. Instead, all patients who became candidates for accrual in the trial after the results of the SPIRITS trial were publicized were to be informed of the novel standard treatment in Japan, using a newly compiled explanatory note, and they were to be offered the alternative of receiving the combination therapy instead of participating in the trial. Each participating institution agreed on the use of the newly compiled explanatory note without correction in the study protocol itself, and case recruitment was re-started after the IRB approval of the amendment was obtained.

Results

A total of 161 patients were enrolled in the trial from December 2005 to November 2008. The numbers of patients in arms A, B, C, and D were 40, 40, 41, and 40, respectively. Two patients in arm A and two in arm C declined therapies before the start of the assigned treatment. Therefore, 38, 40, 39, and 40 patients in arms A, B,

C, and D, respectively, were considered to be eligible for evaluation (Fig. 1). Initial patient characteristics in the four arms were well matched (Table 1). The median age was 67 years (range 40–90 years).

Survival

The ten-month OS rates predetermined as the primary endpoint were 63, 65, 61, and 73% in arms A, B, C, and D, respectively. Although concurrent therapy with S-1 plus PTX demonstrated the best survival benefit among the four arms, the difference in OS rates between the arms with highest (D) and lowest (C) rates was less than the predetermined criterion (i.e., 15%). Kaplan–Meier survival curves did not show a significant difference between the four arms (Fig. 2). The survival rates in the sequential (A, B) and concurrent (C, D) arms were almost identical ($p = 0.93$) (Fig. 3a). In addition, no difference in survival was observed between the 5-FU-containing regimens (arms A and C) and the S-1-containing regimens (arms B and D) ($p = 0.83$) (Fig. 3b).

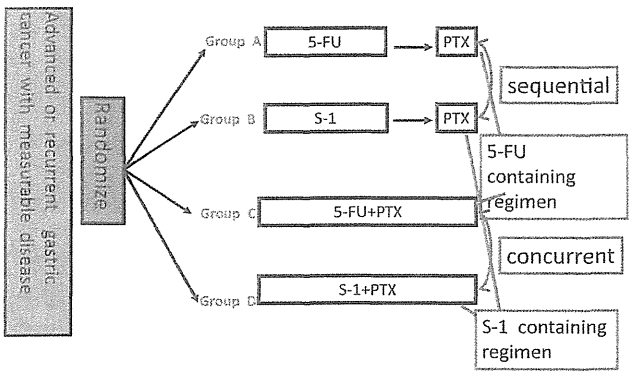

Fig. 1 CONSORT diagram that accounts for all patients. *5-FU* 5-fluorouracil, *PTX* paclitaxel

Time to treatment failure (TTF)

In arms A and B, TTF was calculated by the addition of the prior 5-FU or S-1 treatment period and the sequential PTX period. Median TTF values were 213, 222, 177, and 189 days in arms A, B, C, and D, respectively. No difference was observed between the four arms. However, Kaplan–Meier TTF curves for sequential and concurrent regimens showed better TTF in favor of sequential treatment compared with concurrent treatment (HR 0.71, 95%

Table 1 Patient characteristics

Treatment arm	Arm A 5-FU→PTX $n = 38$	Arm B S-1→PTX $n = 40$	Arm C 5-FU+PTX $n = 39$	Arm D S-1+PTX $n = 40$
Gender				
Male	25 (65.8%)	28 (70.0%)	28 (71.8%)	32 (80.0%)
Female	13 (34.2%)	12 (30.0%)	11 (28.2%)	8 (20.0%)
Age (years)				
Median	67.0	68.0	67.3	66.6
Range	48–79	51–81	40–82	47–90
74≤	31 (81.6%)	33 (82.5%)	31 (79.5%)	31 (77.5%)
≤75	7 (18.4%)	7 (17.5%)	8 (20.5%)	9 (22.5%)
Performance status				
0	29 (76.3%)	27 (67.5%)	25 (64.1%)	28 (70.0%)
1	9 (23.7%)	13 (32.5%)	14 (35.9%)	12 (30.0%)
Stage				
Non-resectable, no previous chemotherapy	31 (81.6%)	33 (82.5%)	32 (82.1%)	32 (80.0%)
Recurrent after curative surgery, adjuvant chemotherapy (+)	2 (5.3%)	1 (2.5%)	3 (7.7%)	3 (7.5%)
Recurrent after curative surgery, adjuvant chemotherapy (–)	5 (13.2%)	6 (15.0%)	4 (10.3%)	5 (12.5%)
Peritoneal metastasis				
Yes	9 (23.7%)	13 (32.5%)	5 (12.8%)	10 (25.0%)
No	29 (76.3%)	27 (67.5%)	34 (87.2%)	30 (75.0%)
Measurable disease				
Yes	19 (50.0%)	23 (57.5%)	17 (43.6%)	20 (50.0%)
No	19 (50.0%)	17 (42.5%)	22 (56.4%)	20 (50.0%)

5-FU 5-fluorouracil, *PTX* paclitaxel

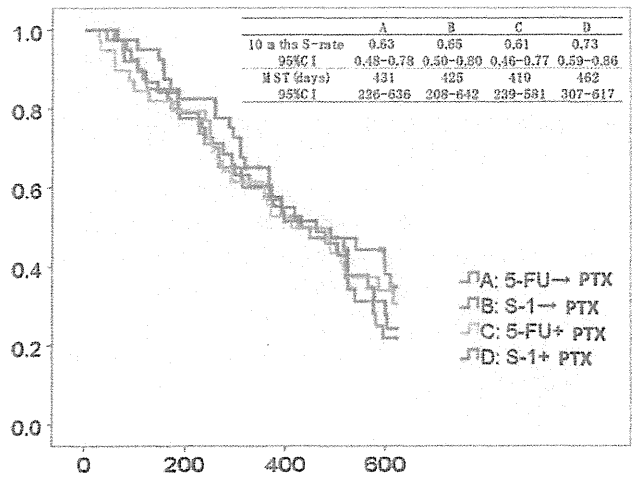

Fig. 2 Kaplan–Meier plot of overall survival in the four treatment arms. *S-rate* survival rate, *CI* confidence interval, *MST* median survival time

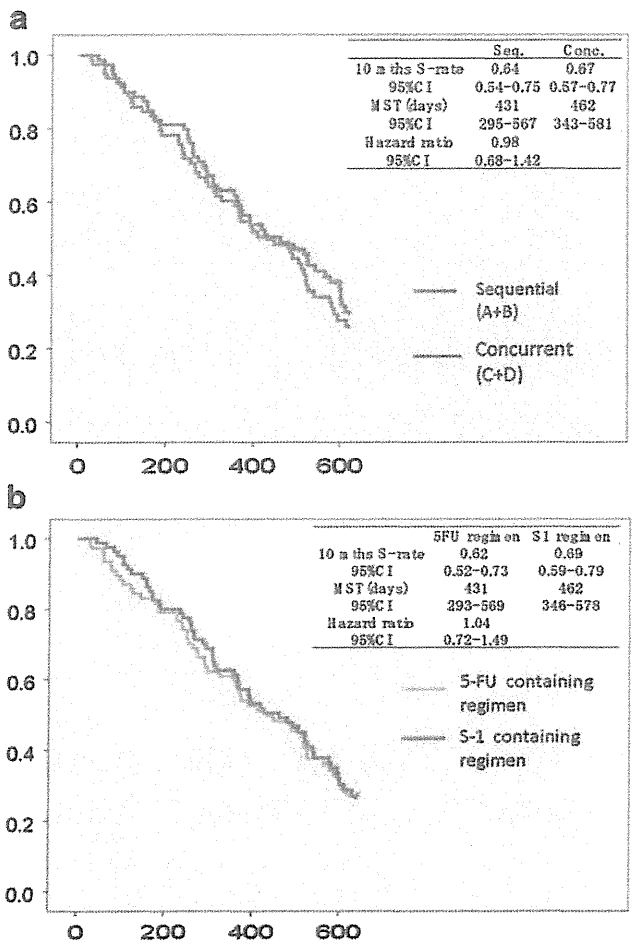

Fig. 3 Kaplan–Meier plot of overall survival by **a** sequential regimens (arms *A* and *B*) and concurrent regimens (arms *C* and *D*), **b** 5-FU-containing regimens (arms *A* and *C*) and S-1-containing regimens (arms *B* and *D*). *seq.* sequential, *conc.* concurrent

Table 2 Tumor response rates

Treatment arm/agent	*n* (With measurable lesion)	CR	PR	SD	PD	Response rate (%)
A						
5-FU	17	0	5	8	4	29.4
PTX	17	0	2	10	5	11.8
B						
S-1	20	1	4	10	5	25.0
PTX	14	1	1	10	2	14.3
C						
5-FU + PTX	13	0	9	2	2	69.2
D						
S-1 + PTX	19	1	7	11	0	42.1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

confidence interval [CI] 0.50–1.02, $p = 0.06$). A difference in TTF was not observed between the 5-FU-containing and S-1-containing regimens.

Response rates

The overall response rates in patients who had measurable disease are summarized in Table 2. Response rates were higher in the concurrent arms than in the sequential arms. The 5-FU and PTX combination regimen showed the best response rate among the four arms.

Toxicities

All patients could be assessed for hematological and non-hematological toxicities (Table 3). Ten of 78 patients (12.8%) who received sequential therapy and 26 of 79 patients (33.0%) who received concurrent therapy showed grade-3 or grade-4 neutropenia. With respect to hemoglobin decrease, 21 patients (26.2%) with the S-1-containing regimens showed grade-3 or grade-4 adverse events, whereas only 8 patients (10.4%) with the other regimens showed adverse events. No difference was observed in non-hematological toxicity.

Compliance

Compliance with S-1 treatment was inferior to that with 5-FU treatment. The median numbers of courses accomplished in the first- and second-line treatment of the