Table IV. *Frequency of treatment-related toxicity (CTCAE Ver.3 common toxicity criteria).*

Toxicity	Dose level			
	1 N=3	2 N=3	3 N=3	4 N=5
Hematologic				
Febrile neutropenia	0	0	0	2 (grade 3)
Leucopenia	0	0	0	2 (grade 3)
Anemia	0	1 (grade 2)	1 (grade 2)	0
Thrombocytopenia	0	0	1 (grade 2)	0
Nonhematologic				
Anorexia	3 (grade 2)	3 (grade 2)	2 (grade 2)	1 (grade 2)
Fatigue	1 (grade 2)	0	1 (grade 2)	1 (grade 2)
Mucositis	0	0	1 (grade 1)	1 (grade 2)
Nausea/vomitting	1 (grade 2)	1 (grade 2)	1 (grade 1)	1 (grade 2)
Diarrhea	0	1 (grade 2)	1 (grade 1)	0
Pericardial effusion	0	0	1 (grade 1)	0 (grade 1)
Alopecia	2 (grade 1)	1 (grade 1)	2 (grade 1)	2 (grade 1)
	1 (grade 2)	2 (grade 2)	1 (grade 2)	2 (grade 2)
Edema	0	1 (grade 2)	1 (grade 2)	1 (grade 2)
Hypersensitivity reaction	0	1 (grade 2)	0	0

patients (14.3%). The prophylactic administration of L-glutamine may have helped to prevent mucositis. Four out of 72 courses of chemotherapy (5.6%) were delayed for one week due to myelosuppression.

Tumor response. Although the endpoint of this study was not response to therapy, patients who had completed at least two cycles of chemotherapy were evaluated for radiographical response. Five patients showed complete response: three patients received two cycles for a locally advanced esophageal cancer and underwent complete resection (histological grade 2 in one patient and grade 3 in two patients), and two patients received 6-10 cycles for metastatic esophageal cancer (lung and bone, one patient; liver, one patient). Of the six patients with partial response, three stopped therapy after receiving two cycles and underwent surgical curative resection. Three patients with partial response and two patients with stable disease for metastatic esophageal cancer maintained disease stability over 4-7 treatment cycles. One patient had documented stable disease after two cycles for locally advanced esophageal carcinoma and underwent complete resection (histological grade 1).

The response rate was 78.6%, with five patients achieving a complete response and six patients a partial response. Disease stability was observed in the remaining three patients, and no disease progression was observed. No patient discontinued study therapy due to toxicity. Responses were observed at all dose levels, indicating a wide margin of activity for this regimen.

Here, we present a case of complete response to this regimen. The patient was a 72-year-old man who underwent curative resection for advanced esophageal carcinoma (T4N3M0; stage IVa) after receiving the level 2 regimen. Endoscopy revealed an invasive, ulcerative-type cervical esophageal tumor (Figure 1). Biopsy confirmed the diagnosis of SCC. Esophagography showed a circumferential stricture (longest diameter, 55.5 mm) (Figure 2). Invasion of the bronchus by the tumor was suspected on CT (Figure 3). Ultrasonography of the neck showed a round supraclavicular lymph node 12 mm in diameter, which was considered to be a metastatic lesion. Two courses of DGS chemotherapy were undertaken in an attempt to down-stage the tumor. Grade 2 diarrhea was observed. After resolution of toxicity, a three-hole esophagectomy with cervical and mediastinal lymph adenectomy was performed. Following resection, the esophageal cancer was determined to be T0N0M0, stage 0. Histopathological examination of the resected specimen showed an excellent response to the preoperative chemotherapy (Figure 4). The supraclavicular lymph nodes showed fibrosis, strongly suggesting that lymph node metastases had also responded to chemotherapy.

Discussion

Survival time in patients with advanced esophageal cancer is unsatisfactory, and locoregional recurrence and wide metastatic spread remain common in spite of the development of operative procedures and improvement in staging

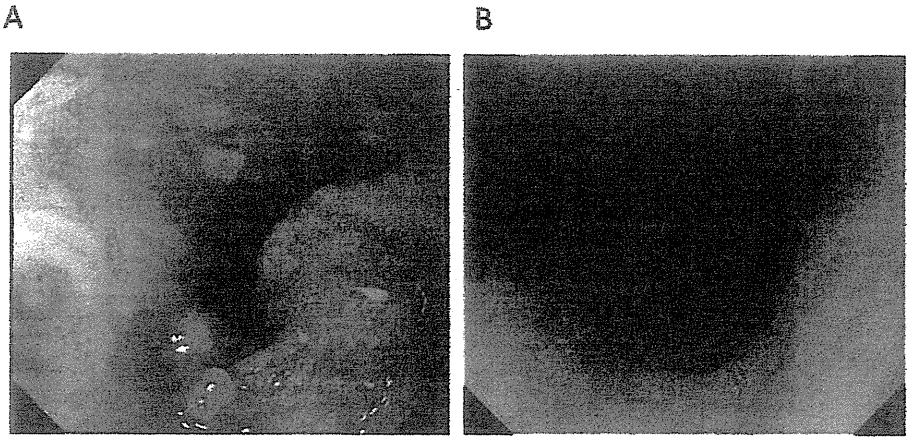

Figure 1. *Endoscopic findings showing an invasive, ulcerative-type cervical esophageal tumor before treatment (A); After chemotherapy (B).*

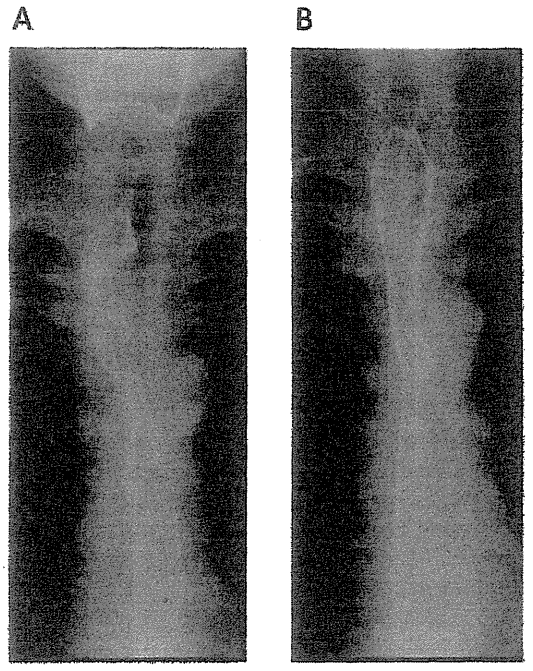

Figure 2. *Esophagographic findings showing circumferential stricture (longest diameter, 55.5 mm) before treatment (A) and after chemotherapy (B).*

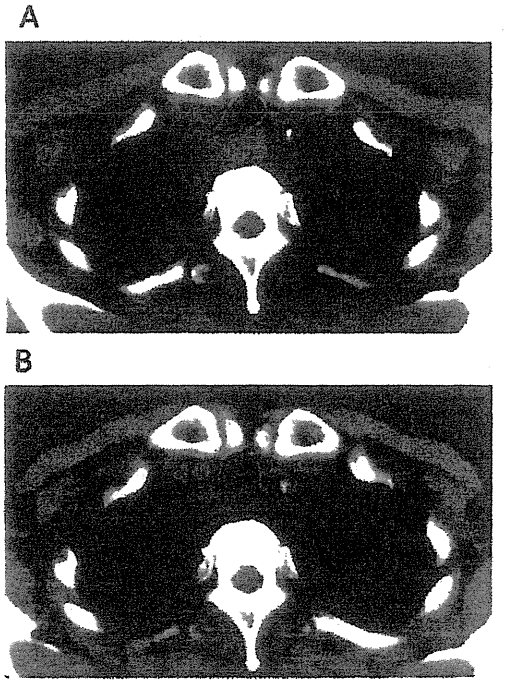

Figure 3. *A: Invasion of the bronchus by tumor was suspected on computed tomography (CT) before treatment. B: After chemotherapy.*

modalities, surgical techniques, and perioperative management (22). Although morbidity and mortality after surgical treatment for advanced esophageal cancer have been reduced and the rate of complete resection has increased, 5-year survival after curative surgery is still only 20-36% (23). There is much evidence that effective chemotherapy for treatment of distant metastasis of esophageal cancer does not exist, and it necessary to establish chemotherapy that considers toxicity in those patients in whom global body function deteriorates during therapy. Therapy is needed that can be delivered as much as possible *via* the outpatient setting to maintain high quality of life and that can be achieved without the necessity of a large amount of fluid infusion or continuous intravenous administration, both of which require hospitalization.

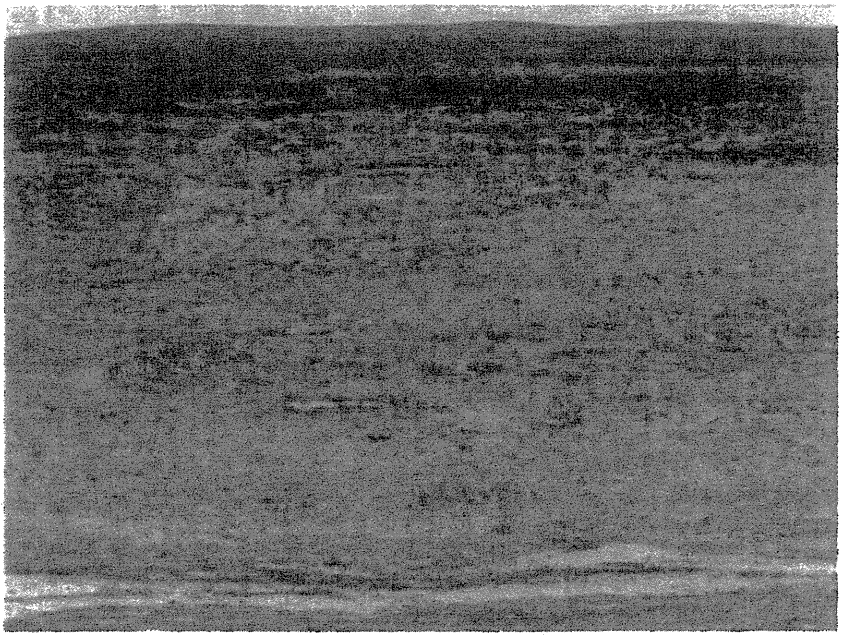

Figure 4. *Histophathological examination of the resected specimen showed an excellent response to the pre-operative chemotherapy.*

Thus, the present study was designed to establish a safe and tolerable dose of docetaxel when administered in combination with fixed doses of nedaplatin and S-1. Docetaxel (Taxotere; Sanofi-Aventis, Paris, France) is a semi-synthetic taxoid derived from the European yew, *Taxus baccata*. The taxanes enhance polymerization of tubulin into stable microtubule formation and inhibit their tubulin depolymerization by blocking the cell cycle in metaphase, anaphase and interphase (24). The synergistic effects of nedaplatin and fluorouracil have been reported *in vivo* (25), and S-1 is also expected to enhance the antitumor effect of nedaplatin.

The intervals at which these three medicines can be administered has been a problem. Cisplatin showed the best activity when given 8 days after the start of daily uracil-tegafur-cisplatin administration (26). Therefore, Koizumi *et al*. reported that they administered cisplain on day 8 of a 21-day consecutive S-1 administration in patients with gastric cancer (27). Docetaxel offers favorable outcomes, although it has adverse hematological toxicity. Neutropenia occurs approximately 8-10 days after administration but recovers rapidly (28, 29).

On the basis of these reports and to minimize toxicity and maximize dose intensity, we elected to investigate a regimen of an infusion of docetaxel and fixed dose of nedaplatin (40 mg/m^2) on day 8 plus oral administration of a fixed dose of S1 (80 mg/m^2/day) for two consecutive weeks at two-week intervals. In the present study, 72 courses of chemotherapy were administered in total to the 14 patients, and responses were observed at all dose levels. No treatment-related deaths were observed. Toxicity of docetaxel was encountered at all dose levels, indicating that the pharmacokinetics of this drug may vary in different individuals.

The median white blood cell and platelet count nadirs occurred on day 18 (range 9 to 20 days), with a median hematological recovery observed by day 24. Neutropenic fever requiring hospitalization was observed in two patients. One patient had grade 2 anemia that did not require blood transfusion, and no thrombocytopenia ≥grade 3 was seen.

The incidence of docetaxel-specific toxicities, such as acute hypersensitivity reactions and neurotoxicity, was relatively low and did not appear to be a major clinical problem, so a reduction in dose was generally not required. Fluid retention manifesting as peripheral edema, pleural effusion, or ascites was cumulative in incidence and severity. Three patients had grade 2 edema that required diuretics.

Patients receiving more than 50 mg/m^2 of cisplatin may suffer nausea and vomiting (30). Few patients experience these side-effects with nedaplatin, and they can be well controlled by administration of granisetron and dexamethasone. Grade 1/2 alopecia was observed in 13/14 patients in the present study. Of note, no patient in our study experienced grade 3 or 4 mucositis, likely due to the great care paid to daily oral supplementation with L-glutamine, which contributed to the low toxicity profile of this regimen.

Finally, all seven patients with locally advanced esophageal carcinoma underwent radical surgical resection, no postoperative mortality. Pathologically confirmed complete response was documented in two patients. Toxicities associated with this regimen did not interfere with planned radical surgery.

Locoregional disease control was achieved in 12/14 and distant disease control was achieved in 10/14 of the patients in the present study. The results emerging from this phase I study are particularly encouraging. We want to strongly emphasize that we were able to administer DGS combination therapy in the outpatient setting to all but the two patients with digestive obstruction. Eventually, however, these two patients were also able to take all drugs orally, and we were able to administer the third course of therapy to these patients in an outpatient setting.

In the present study, 11 patients were diagnosed as having SCC, whereas most esophageal carcinomas in Western populations are diagnosed as adenocarcinoma (31). Responses of the three patients diagnosed as having esophageal adenocarcinoma in this study were one complete, one partial, and one stable disease. This DGS regimen appeared to be effective for adenocarcinoma.

In conclusion, the recommended DGS combination dose in the present study was determined to be docetaxel at 35 mg/m^2 with nedaplatin at 40 mg/m^2 on day 8 plus oral administration of S1 (80 mg/m^2/day) for two consecutive weeks at two-week intervals. Our regimen showed high activation and tolerance. It not only could be offered as a candidate component of new standard regimens for treating advanced esophageal carcinoma but may also be acceptable as a second-line regimen, even in cases of deteriorated renal function induced by several chemotherapies. Furthermore, the merit of this regimen to the patients and their families is that it can be administered in an outpatient setting. A phase II study has already begun. Further clinical trials of this combination therapy should be pursued in the treatment of advanced esophageal carcinoma.

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ORIGINAL PAPER

Evaluation of efficacy and safety of generic levofolinate in patients who received colorectal cancer chemotherapy

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Abstract The efficacy and safety of generic and brand name levofolinate injectable drugs were evaluated in 42 chemotherapy-naïve patients with colorectal cancer who received the combination chemotherapy of levofolinate, 5-fluorouracil, and oxaliplatin with or without bevacizumab. The tumor response rate was similar between generic drug group and brand drug group, in which the efficacy rate (complete response plus partial response) was 50% for generic drug group and 42% for brand name drug (odds ratio: 1.400, 95% confidence intervals: 0.409–4.788, $P = 0.756$). The rates of the decrease in plasma tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19-9 were not different between the two groups. The incidence of adverse drug reactions was not significantly different between the two groups, although the incidence rates of adverse events associated predominantly with 5-fluorouracil such as hand-and-foot syndrome, diarrhea, and oral mucositis were rather higher, though not significantly, in generic drug group than in brand drug group (16 vs. 4% for hand-and-foot syndrome; 33 vs. 25% for diarrhea; 33 vs. 25% for oral mucositis). These findings suggest that both the effectiveness and safety profiles of the generic name levofolinate are comparable to those of the brand name drug, when used in combination with 5-fluorouracil and oxaliplatin in patients with colorectal cancer.

Keywords Anticancer drug · Levofolinate · Generic drug · Efficacy · Safety · Colorectal cancer

Introduction

The use of generic name drugs has been promoted all over the world to save the medical costs; however, the frequency of prescription of generic drugs is still much lower in some Asian countries including Japan than in the Western countries. This low penetration rate is due to a number of reasons, including limited provision of drug information from manufacturers of generic drugs, difficulties for some manufacturers in the system for securing a stable supply of generic drugs, and the lack of data showing the clinical efficacy and safety of generic drugs. In the case of oral drugs, the conditions for approval of generic drugs are specifications testing, stability study, dissolution test, and a bioequivalence study showing the equivalence with the brand drug regarding clinical pharmacokinetics (AUC and C_{max}) [1]. However, such a bioequivalence study is not applied to the injectable drugs. Therefore, some medical practitioners may feel reluctant to use the injectable generic drugs.

Although a number of investigators have shown the stability, physicochemical properties or adverse drug reactions of generic drugs in comparison with the brand name drugs, few studies have compared clinical efficacy as well as safety between brand and generic drugs.

In December 2008, our hospital switched from Isovorin® Injection (Wyeth Pharmaceuticals, Japan), the brand name levofolinate (l-LV) injectable drug, to the generic drug Levofolinate® for I.V. Infusion (Nippon Kayaku Co., Ltd., Japan). It has been shown that l-LV enhances the effect of 5-fluorouracil (5-FU) as a result of biochemical modulation [2], and thus the agent is frequently used in the chemotherapy

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regimens including 5-FU for colorectal cancer (e.g., 5-FU/l-LV combination therapy [3, 4], FOLFOX [5, 6], FORFIRI [7–9]). In addition, the therapeutic effects of FOLFOX therapy and FOLFIRI therapy can be enhanced by administration in combination with the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (BV) [10, 11]. It should be noted that, in Japan, modified FOLFOX6 (mFOLFOX6) therapy is widely used, in which the dose of oxaliplatin (l-OHP) is reduced from 100 mg/m^2 in FOLFOX6 regimen to 85 mg/m^2 [11–13]. Therefore, the present study was designed to compare the effectiveness and the incidence of adverse drug reactions in chemotherapy-naïve patients with colorectal cancer undergoing mFOLFOX6 or BV + mFOLFOX6 combination chemotherapy using l-LV brand or generic drug.

Patients and methods

A total of 42 chemotherapy-naïve outpatients with metastatic colorectal cancer who received mFOLFOX6 or BV + mFOLFOX6 combination therapy at the outpatient chemotherapy unit of our hospital were included. The brand drug group ($N = 24$) received treatment at this hospital from December 2007 to November 2008 and the generic drug group ($N = 18$) from December 2008 to September 2009.

An infusion port was implanted subcutaneously below the clavicle at the first chemotherapy session, and for patient safety, patients were hospitalized. mFOLFOX6 [12, 13] or FOLFOX6 modified by Maindrault-Goebel et al. [14] was administered as chemotherapy. A 2-h intravenous infusion of l-OHP (85 mg/m^2) and l-LV (200 mg/m^2) was followed by intravenous administration of 5-FU (400 mg/m^2). A 46-h continuous intravenous infusion of 5-FU (2,400 mg/m^2) was also administered using an infuser. This treatment protocol constituted one course and was repeated at 14-day intervals. It should be noted that, in the combination of BV + mFOLFOX6, BV (5 mg/kg) was administered intravenously over 2 h before the initial course of chemotherapy, 1 h before the 2nd course, and 30 min before the 3rd and subsequent courses [10, 11].

The tumor response rate and change in plasma tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 were assessed as indicators of the efficacy. The tumor response rate at the initial efficacy evaluation was compared. The efficacy was evaluated on computed tomography (CT) scan as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. The efficacy rate was defined as CR + PR, while the disease control rate as CR + PR + SD.

Moreover, tumor markers, including CEA and CA19-9, were used as indicators of the efficacy, and the ratio of patients whose tumor marker levels in plasma were lowered at the initial efficacy evaluation compared to the baseline values was determined.

The incidence of adverse drug reactions associated with mFOLFOX6 therapy and BV + mFOLFOX6 therapy was compared between the brand and generic drug groups. Specifically, the adverse drug reactions investigated were hematological toxicities such as neutropenia, leukopenia, anemia and thrombocytopenia, and non-hematological toxicities, including peripheral neuropathy, anorexia, nausea, vomiting, taste disturbance, constipation, oral mucositis, hand-and-foot syndrome, and diarrhea. It should be noted that the severity of adverse drug reactions was graded in accordance with the Common Terminology Criteria for Adverse Events, version 3.0, Japan Clinical Oncology Group/Japan Society of. Clinical Oncology (CTCAE v3.0 JCOG/JSCO) (Japanese edition, 2007).

Data were statistically analyzed using the statistic program for social science for Windows (SPSS II, ver. 11, SPSS, Inc.). For patient information, the *t*-test was used for hematology values, body surface area, and dose of anti-cancer agent, the Mann–Whitney *U* test for age, and Fisher's exact probability method for all other data. Response rates, response rates based on tumor markers, and incidence of adverse drug reactions were compared using Fisher's exact probability method. Differences were considered to be statistically significant when *P*-value was less than 0.05.

Results

Table 1 shows a comparison of profiles between generic and brand name l-LV injectable drugs. The additives and properties were the same for both preparations.

As shown in Table 2, no significant differences were observed between the treatment groups for any patient background parameter such as gender, age, body surface area, dose of each anti-cancer agent, and hematology values. For patients who received mFOLFOX6 therapy, the brand drug group consisted of 12 patients and the generic drug group consisted of 11 patients. Similarly, for patients who received BV + mFOLFOX6 therapy, the brand drug group consisted of 12 patients and the generic drug group consisted of 7 patients.

Efficacy evaluation

The tumor response rates in the two groups were shown in Table 3. The rates of CR [11% (2/18) for generic drug group versus 0% (0/24) for brand drug group, $P = 0.178$],

Table 1 Quality comparison between brand name and generic preparations of levofolinate for injection

	Generic name	Brand name
	Levofolinate for I.V. Infusion 25 mg [NK]	Isovorin® Injection 25 mg
	Levofolinate for I.V. Infusion 100 mg [NK]	Isovorin® Injection 100 mg
Manufacturer	Nippon Kayaku Co. Ltd.	Wyeth
Additives	D-Mannitol 25 mg/100 mg	D-Mannitol 25 mg/100 mg
	Hydrochloric acid s.q.	Hydrochloric acid s.q.
	Sodium hydroxide s.q.	Sodium hydroxide s.q.
Description	Light yellowish white powder or lumps	Light yellowish white powder or lumps
pH	6.8–8.2 (I-LV 10 mg/mL injection solvent)	6.8–8.2 (I-LV 10 mg/mL injection solvent)
Drug price	1,871 yen, $21.0 (25 mg)	2,864 yen, $32.2 (25 mg)
	6.905 yen, $77.6 (100 mg)	10,148 yen, $114.0 (100 mg)

Table 2 Patient characteristics

	Generic name	Brand name	*P* value
No. of patients (male/female)	18 (15/3)	24 (17/7)	0.473[a]
Age (range)	64.3 (40–78)	63.8 (42–86)	0.715[b]
Body surface area (m^2)	1.67 ± 0.20	1.61 ± 0.21	0.513[c]
Aspartic aminotransferase (U/l)	24.8 ± 9.4	27.1 ± 16.5	0.600[c]
Alanine aminotransferase (U/l)	28.2 ± 13.9	27.8 ± 18.8	0.950[c]
Total Bilirubin (g/dl)	0.7 ± 0.4	0.8 ± 0.3	0.754[c]
Serum creatinine (mg/dl)	0.7 ± 0.2	0.7 ± 0.2	0.690[c]
Blood urea nitrogen (mg/dl)	13.6 ± 5.9	12.7 ± 5.0	0.613[c]
Neutrophil ($10^3/mm^3$)	4.42 ± 1.93	4.42 ± 1.47	0.992[c]
White blood cells (mm^3)	6,716 ± 1953	6,735 ± 1677	0.974[c]
Hemoglobin (g/dl)	12.2 ± 1.7	11.7 ± 1.6	0.299[c]
Platelet ($10^3/mm^3$)	279 ± 123	294 ± 117	0.692[c]
Performance status			
0	16	22	1.000[a]
1	0	1	1.000[a]
2	2	1	0.579[a]
Chemotherapy courses	9.3 ± 2.9	9.6 ± 4.1	0.713[a]
Doses of anticancer drugs			
5-Fluorouracil (mg/body)	4,597 ± 622	4,285 ± 714	0.147[c]
L-leucovorin (mg/body)	335 ± 40	322 ± 41	0.314[c]
Oxaliplatin (mg/body)	139 ± 20	128 ± 24	0.132[c]
Chemotherapy regimen			
mFOLFOX6 + bevacizumab	7	12	0.541[a]
mFOLFOX6	11	12	

[a] Data represent the mean ± SD. Statistical analysis was carried out by Fisher's exact probability test, [b] Mann–Whitney *U* test or [c] *t*-test

PR [39% (7/18) vs. 42% (10/24), odds ratio (OR) 0.891, 95% confidence intervals (CI) 0.256–3.102, $P = 1.000$], SD [33% (6/18) vs. 38% (9/24), OR 0.833, 95% CI 0.231–3.003, $P = 1.000$] and PD [11% (2/18) vs. 13% (3/24), OR 0.875, 95% CI 0.130–5.872, $P = 1.000$] were not significantly different between the two groups. Moreover, the efficacy rate defined as CR plus PR (50 vs. 42%, OR 1.400, 95% CI 0.409–4.788, P = 0.756) and the disease control rate defined as CR plus PR plus SD (83 vs. 79%, OR 1.316, 95% CI 0.270–6.410, $P = 1.000$) were also similar between the two groups.

The rates of decrease in CEA in the generic and brand drug groups were 44% (8/18) and 54% (13/24), respectively, with no significant difference noted between the groups ($P = 0.755$). The incidence of the decrease in CA19-9 in the generic and brand drug groups was 61% (11/18) and 46% (11/24), respectively, with no significant difference noted between the groups ($P = 0.367$).

Table 3 Comparison of the tumor response rates and the rate of the decrease in plasma tumor markers after mFOLFOX6 (±bevacizumab) therapy using generic or brand name levofolinate injectable drug in patients with colorectal cancer

	Generic name ($N = 18$)	Brand name ($N = 24$)	P value	OR	95% CI
Response rates (%)					
Complete response (CR)	11.1	0	0.178	–	–
Partial response (PR)	38.9	41.7	1.000	0.891	0.256–3.102
Stable disease (SD)	33.3	37.5	1.000	0.833	0.231–3.003
Progressive disease (PD)	11.1	12.5	1.000	0.875	0.130–5.872
Not assessable (NA)	5.6	8.3	1.000	0.647	0.054–7.746
Efficacy rate (CR + PR)	50.0	41.7	0.756	1.400	0.409–4.788
Disease control rate (CR + PR + SD)	83.0	79.2	1.000	1.316	0.270–6.410
Patients showing a decrease in tumor markers (%)					
CEA	44.4	54.2	0.756	0.677	0.198–2.312
CA19-9	44.4	45.8	0.367	1.857	0.536–6.431

Data were statistically analyzed by Fisher's exact probability test. Odds ratio (OR) and 95% confidence intervals (CI) were indicated

Incidence of adverse drug reactions

Table 4 shows the incidence of hematological and non-hematological toxicities associated with mFOLFOX6 or BV + mFOLFOX6 therapy. A comparison of hematological toxicities (all grades) between the generic and brand name drug groups showed that neutropenia was 61% and 67% ($P = 0.754$), leukopenia was 67% and 54% ($P = 0.530$), decrease in hemoglobin was 72% and 88% ($P = 0.256$), and thrombocytopenia was 78% and 67% ($P = 0.506$), respectively.

The frequently occurred non-hematological toxicities included peripheral neuropathy, anorexia, nausea, taste disturbance, constipation, oral mucositis, hand-and-foot syndrome, and diarrhea. The incidence rates of peripheral neuropathy (88 vs. 61%; $P = 0.07$), anorexia (71 vs. 72%, $P = 1.00$), nausea (46 vs. 50%, $P = 1.00$), and constipation (25 vs. 11%, $P = 0.431$) were not significantly different between the two groups. The incidence rates of adverse events associated predominantly with 5-fluorouracil such as oral mucositis (33 vs. 25%, $P = 0.732$), hand-and-foot syndrome (16 vs. 4%, $P = 0.623$), and diarrhea (33 vs. 25%, $P = 0.732$) were comparable or even higher, though not significantly, in generic drug than in brand name drug. In addition, the incidence rates of Grade >2 oral mucositis (17 and 0%, $P = 0.064$) and diarrhea (11 and 4%, $P = 0.567$) also tended to be higher in the generic drug group.

Discussion

In the present study, the efficacy and safety of mFOLFOX6 therapy with or without bevacizumab using generic name or brand name l-LV were compared in patients with colorectal cancer. The efficacy was evaluated using RECIST-based response rates as indicators [15]. In a previous study reported by Shimizu et al. [12] in 31 patients with metastatic colorectal cancer who received mFOLFOX6 therapy, the response rates were CR 0%, PR 36%, SD 42%, and PD 23%. In another study by de Gramont et al. [5] in 210 patients with inoperable colorectal cancer, the response rates following FOLFOX4 (l-OHP dose: 85 mg/m^2) were CR 1.4%, PR 49%, SD 32%, and PD 10%. Similar response rates (CR 0%, PR 42%, SD 38%, and PD 13%) were also obtained in our study in the l-LV brand drug group. The efficacy rate (CR + PR, 42%) and disease control rate (CR + PR + SD, 79%) obtained in the present study in brand name drug group were also generally consistent with those reported earlier. The response rates in generic drug group were comparable or even higher, though not significantly, than those in the brand name drug group, in which CR 11%, PR 39%, SD 33%, and PD 11%, with an efficacy rate of 50% and disease control rate of 83%. There was also no significant difference in the efficacy rate based on the decrease in plasma tumor markers such as CEA and CA19-9 between the two groups.

The non-hematological adverse drug reactions frequently observed following therapy in this study were peripheral neuropathy, anorexia, nausea, and vomiting. The main etiological factor in these toxicities is presumed to be l-OHP, since l-OHP causes acute and chronic peripheral neuropathy [16–18], a dose-limiting factor. In addition, l-OHP is classified as the moderate emetic risk anticancer agent, while 5-FU is a low emetic risk agent, according to the National Comprehensive Cancer Network (NCCN) Antiemesis Guidelines [19]. de Gramont et al. [5] reported that the incidence of peripheral neuropathy (all grades) is markedly elevated by the addition of l-OHP to the

Table 4 Comparison of the incidence of hematological and non-hematological adverse drug reactions (ADRs) associated with mFOLFOX6 (±bevacizumab) therapy using generic or brand name levofolinate injectable drug in patients with colorectal cancer

	Generic name ($N = 18$)		Brand name ($N = 24$)		P value
	Patients	%	Patients	%	
All grade					
Hematological toxicities					
Neutropenia	(11/18)	61.1	(16/24)	66.7	0.754
Leukopenia	(12/18)	66.7	(13/24)	54.2	0.530
Anemia	(13/18)	72.2	(21/24)	87.5	0.256
Thrombocytopenia	(14/18)	77.8	(16/24)	66.7	0.506
Non-hematological toxicities					
Peripheral neuropathy	(11/18)	61.1	(21/24)	87.5	0.070
Anorexia	(13/18)	72.2	(17/24)	70.8	1.000
Nausea	(9/18)	50.0	(11/24)	45.8	1.000
Vomiting	(2/18)	11.1	(2/24)	8.3	1.000
Taste disturbance	(10/18)	55.6	(7/24)	29.2	0.117
Constipation	(2/18)	11.0	(6/24)	25.0	0.431
[ADRs associated predominantly with 5-FU]					
Oral mucositis	(6/18)	33.3	(6/24)	25.0	0.732
Hand-and-foot syndrome	(3/18)	16.0	(1/24)	4.2	0.623
Diarrhea	(6/18)	33.3	(6/24)	25.0	0.732
Grade >2					
Hematological toxicities					
Neutropenia	(7/18)	38.9	(4/24)	16.7	0.159
Leukopenia	(1/18)	5.6	(0/24)	0	0.738
Anemia	(0/18)	0	(1/24)	4.2	0.309
Non-hematological toxicities					
Peripheral neuropathy	(10/18)	55.6	(16/24)	66.7	0.531
Anorexia	(9/18)	50.0	(11/24)	45.8	1.000
Nausea	(5/18)	27.8	(7/24)	29.2	1.000
Vomiting	(2/18)	11.1	(0/24)	0	0.178
Taste disturbance	(3/18)	16.7	(2/24)	8.3	0.633
Constipation	(1/18)	5.6	(3/24)	12.5	0.623
[ADRs associated predominantly with 5-FU]					
Oral mucositis	(3/18)	16.7	(0/24)	0	0.064
Diarrhea	(2/18)	11.1	(1/24)	4.2	0.567

Data were statistically analyzed by Fisher's exact probability test

treatment regimen (12% for 5-FU/l-LV therapy vs. 68% for FOLFOX4 therapy). It has also been shown that the incidence of nausea and vomiting associated with FOLFOX4 therapy is significantly increased compared to that associated with 5-FU/l-LV therapy. The incidence (88%) of peripheral neuropathy in the brand drug group in our study was slightly higher than, while the incidence (61%) observed in the generic drug group was similar to that reported by de Gramont et al. [5].

On the other hand, it has been demonstrated that l-LV enhances the effect of 5-FU as a result of biochemical modulation [2, 20]. Therefore, it is presumed that l-LV affects the incidence and severity of 5-FU-related antitumor effect as well as the adverse reactions. Diarrhea, oral mucositis, and hand-and-foot syndrome are typical adverse reactions associated with 5-FU [20, 21]. Interestingly, the incidence of these adverse reactions was even higher, though not significantly, in the generic drug group than in the brand drug group. Briefly, hand-and-foot syndrome (all grades) was 4% in the brand drug group as opposed to 16% in the generic drug group, whereas oral mucositis and diarrhea in the brand and generic drug groups were 25 and

33%, respectively. Similar pattern were observed for Grade >2 oral mucositis (16 vs. 0%, $P = 0.064$) and diarrhea (11 vs. 4%, $P = 0.567$).

Based on these findings, it was suggested that the generic l-LV preparation used in the present study was comparable to the brand drug in terms of the efficacy as well as the safety.

The medical expense for a single mFOLFOX6 treatment using brand drug l-LV is 146,748 yen ($1,648.5) (body surface area: 1.5 m^2), whereas the generic drug represents a 6.6% saving at 137,019 yen ($1,539.2). In the case of 5-FU/l-LV therapy, the cost per course is 38,004 yen ($426.9) for l-LV brand drug, whereas the generic drug is 25.6% less at 28,275 yen ($317.6). Therefore, from a view point of cost effectiveness, the present generic l-LV preparation seemed to be highly useful for the chemotherapy in colorectal cancer.

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Pharmacists contribute to the improved efficiency of medical practices in the outpatient cancer chemotherapy clinic

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Abstract

Rationale, aims and objectives Outpatient cancer chemotherapy is increasing with the development of anticancer agents, and roles of medical staff are becoming more and more important in cancer chemotherapy. We showed here roles of pharmacists with experience in oncology and evaluated outcomes of their activities in medical practices in cancer chemotherapy clinic.

Methods Two pharmacists were newly assigned to the outpatient cancer chemotherapy clinic, where they were in charge of verification of prescription orders, mixing of anticancer injections, monitoring adverse drug reactions, implementation of supportive care and provision of information about cancer chemotherapy to medical staff and patients. The number of patients, amounts of mixing of anticancer injections and hospital revenue were compared before and after assignment of pharmacists. Management of chemotherapy-induced nausea and vomiting in breast cancer patients receiving the combination chemotherapy with anthracycline and cyclophosphamide were also compared.

Results Pharmacists spent 75 hours per month in patient education and adverse drug reactions monitoring, which led to the reduction of the workload of physicians. As a consequence, the number of outpatients and the resultant hospital revenue markedly increased. In addition, facilitation of proper use of anti-emetic drugs led to the improved control of chemotherapy-induced nausea with reducing the cost for anti-emesis by 16%.

Conclusions Pharmacists contributed to the improved efficiency of medical practices.

Introduction

As the increase in the morbidity and mortality associated with cancer all over the world, the number of patients who undertook cancer chemotherapy is increasing. Moreover, cancer chemotherapy has been shifted from inpatient setting to the outpatient setting because of advancements in supportive care measures for cancer. In addition, cancer therapy has become highly specialized and well advanced during recent years, thus the medical care in oncology should be carried out by oncology team consisting of physicians, pharmacists, nurses and other medical staff who have specialized knowledge and skills in oncology [1,2]. However, because of the shortage of physicians who work in the hospital, a number of medical institutions in Japan face challenges in the establishment of such teams to meet the needs of an increasing number of cancer patients.

In Japan, board-certified oncology pharmacy specialist has been accredited in 2006 by the Japanese Society of Hospital Pharmacists [3]. Oncology pharmacy specialist is responsible for a wide variety of pharmaceutical practices in cancer chemotherapy, including review of cancer chemotherapy regimens, verification of prescription orders containing anticancer drugs, mixing anticancer injections in a biohazard safety cabinet, patients' education, monitoring efficacy and adverse drug reactions (ADRs), prevention or alleviation of ADRs, implementation of palliative care and provision of drug information to the medical staff. Several literatures

have shown that oncology pharmacists contribute to safe management and prevention of ADRs associated with cancer chemotherapy [4–6].

In our hospital, two pharmacists with experience in oncology, including an oncology pharmacy specialist, have been newly assigned to the outpatient cancer chemotherapy clinic as full-time staff since April 2008 to provide information about cancer chemotherapy to patients, to verify chemotherapy regimens and to monitor and prevent ADRs associated with anticancer drugs. In the present paper, we showed that such activities of pharmacists in the outpatient cancer chemotherapy clinic enhanced the efficiency of medical practices by reducing the workload of physicians and nurses. Moreover, the outcomes of pharmaceutical intervention to facilitate the use of adequate anti-emetic drugs on the control of chemotherapy-induced nausea and vomiting (CINV) were shown in breast cancer patients who received a combination chemotherapy with epirubicin and cyclophosphamide.

Materials and methods

Subjects

The present study was carried out in accordance with the guidelines for the care for human study adopted by the ethics committee of the Gifu Graduate School of Medicine, and notified by the Japanese government. Patients who undertook cancer chemotherapy in Gifu University Hospital outpatient cancer chemotherapy clinic during April 2007 and March 2009 were the subjects of the present study. The major cancers were colorectal cancer (35.4% and 39.1% during April 2007 and March 2008 and during April 2008 and March 2009 respectively), followed by breast cancer (27.3% and 23.8%), stomach cancer (20.8% and 19.5%), hepatic/pancreatic cancer (7.6% and 6.9%), urologic cancer (3.3% and 5.7%) and oesophageal cancer (4.5% and 2.2%).

Pharmaceutical practices in outpatient chemotherapy and outcome measurement

Medical staff in the outpatient cancer chemotherapy clinic consisted of two physicians who worked concurrently with general medical practice, three nurses and two pharmacists, including one oncology pharmacy specialist, both of whom stayed full-time in the clinic. Since April 2008, pharmacists were involved in verification of prescription orders based on the cancer chemotherapy regimens, providing pharmaceutical care services to patients as show in Fig. 1, monitoring ADRs, offering proposals of prescriptions to physicians regarding supportive care, in the outpatient cancer chemotherapy clinic. Pharmacists also provided drug information to other medical staff.

Before assignment of pharmacists to the cancer chemotherapy clinic (before April 2008), pharmaceutical practices were limited to the verification of prescription orders regarding cancer chemotherapy and the mixing of anticancer injections in the pharmacy division.

To evaluate outcomes of pharmaceutical practices, the number of anticancer injections, number of outpatients who received cancer chemotherapy and the amount of medical income in the cancer chemotherapy clinic were recorded. Data were compared before and after participation of pharmacists in the oncology team.

Intervention to improve anti-emetic control and outcome measure

We focused on the effect of pharmaceutical intervention on the control of CINV in breast cancer patients who received, for the first time, a combination chemotherapy of anthracycline and cyclophosphamide (AC chemotherapy) such as epirubicin (75–100 mg m^{-2}) + cyclophosphamide (500 mg m^{-2}) + 5-fluorouracil (500 mg m^{-2}; FEC) or epirubicin (90 mg m^{-2}) + cyclophosphamide (600 mg m^{-2}; EC). Several clinical practice guidelines for prevention of CINV were disclosed by the Multinational Association of Supportive Care in Cancer [7], the American Society of Clinical Oncology (ASCO) [8] and the National Comprehensive Cancer Network (NCCN) [9]. According to these guidelines, anticancer injections are classified into four categories based on the emetic risk, including high, moderate, low and minimal emetic risks. Thus, different anti-emetic regimens are recommended for cancer chemotherapy with different emetic risks. AC chemotherapy for breast cancer patients is regarded as the high-emetic chemotherapy. According to the ASCO guideline (2006), the combination of three agents, including the i.v. 5-HT_3 receptor antagonist, i.v. dexamethasone and oral ingestion of the neurokinin NK_1 receptor antagonist such as aprepitant, and the combination of oral dexamethasone and aprepitant are recommended for prevention of acute and delayed CINV, respectively, to patients receiving the high-emetic anticancer injection. In the present study, the incidence and the extent of CINV were checked from the electronic medical record and nursing record and compared before (31 patients) and after pharmaceutical intervention (27 patients). Pharmaceutical intervention included the facilitation of prophylactic treatment with anticancer agents according to the clinical practice guidelines for anti-emesis disclosed by the ASCO 2006, although aprepitant was not prescribed because of a lack of availability of this drug in Japan before December 2009. Therefore, patients were encouraged to receive i.v. injection of 5-HT_3 receptor antagonist such as granisetron (3 mg) in combination with dexamethasone sodium phosphate (19.8 mg) 30 minutes before chemotherapy on day 1, followed by an oral ingestion of dexamethasone (8 mg, once a day) in combination with an oral prochlorperazine (5 mg, three times a day) on days 2–4. The use of prochlorperazine for prevention of delayed CINV was based on the following finding: oral prochlorperazine, when treated on days 2 and 3, is reported to be more effective than 5-HT_3 receptor antagonists in reducing the incidence of delayed nausea in patients receiving doxorubicin-containing chemotherapy [10]. When the emetic control was incomplete in the first course, other anti-emetic agents such as antihistaminic drugs and benzodiazepines were added on the following courses. The rates of control of nausea, vomiting and complete response (no nausea, no vomiting without rescue treatment) during acute (within 24 hours), delayed (24–120 hours) and overall periods (0–120 hours) in the first course of the chemotherapy were determined. Characteristics of patients were shown in Table 1.

Statistical analysis

Data were all analysed using Statistics Program for Social Science for Windows (SPSS X, version 11, SPSS Incorporated, Chicago, IL, USA). Patients' characteristics before and after interventions

Record of pharmaceutical care practices

Patient's ID No.: xxxxxx Gender: male

Patient's name: xxxxxx Date of birth: xx/xx/19xx

Ward or section: gastrointestinal surgery

Name of pharmacist: xxxxx xxxx

Date of patient's education: 16/6/2008

Patient's drug adherence: good

Cancer Diagnosis (Stage): Rectal cancer (stage IV)

Chemotherapy: BV+XELOX (2nd course)

Other prescriptions: granisetron (3 mg i.v., day 1), dexamethasone (12 mg i.v., day 1), dexamethasone (8 mg, days 2, 3), magnesium oxide (1 g oral, t.i.d.), senna

Comments

S: Appetite decreased after chemotherapy.

O: Height 153.8 cm, Weight 47.7 kg, Body Surface Area 1.430 m^2

Bevacizumab (7.5 mg kg^{-1}): 360 mg per body (day 1 = 16 June)
Oxaliplatin (130 mg m^{-2}): 185 mg per body (day 1 = 16 June)
Capecitabine (2000 mg m^{-2}): 1500 mg b.i.d. (days 1–14 = 16 June–29 June)
Interval: 21 days (16 June–5 July)
HTN(-), DM (-)

BP: 123 mmHg/86 mmHg; HR: 82 b $minute^{-1}$; Proteinuria (-); INR: 0.87;
D-dimer <0.7; AST: 29; ALT: 22; Cr: 0.56; T-Bil: 0.7; Neut: 1870; WBC: 3440
Hb: 12.1; Plt: 16.7; CCr: 93.6 mL $minute^{-1}$ (Cockcroft–Gault formula)

A: Delayed nausea: grade 2 (days 3–5)
There was delayed nausea possibly because of oxaliplatin
Add Prochlorperazine 5 mg t.i.d.

P: Check nausea and vomiting

Figure 1 Representative form of record of pharmaceutical care practices in the outpatient cancer chemotherapy clinic. Comments included subjective data (S), objective data (O), assessment (A) and plan to the subsequent intervention (P).

were statistically compared by Mann–Whitney *U*-test for non-parametric data or *t*-test for parametric data. Data on anti-emesis were statistically analysed by Fisher's exact probability test for anti-emesis.

Results

Pharmaceutical practices in the outpatient chemotherapy clinic

As shown in Fig. 2a, the number of patient education, including provision of drug information about cancer chemotherapy and supportive care and ADR monitoring, increased every month. The average time spent in patient education was 32.3 minutes per patient, and annual number of patient education was 1679 cases during 1 year before assignment of pharmacists, indicating that pharmacists carried out patient education for 75 hours in 1 month (31% of total hours) and 904 hours in 1 year. The numbers of proposals of prescriptions for supportive care (Fig. 2b) also gradually increased. The most frequently encountered supportive care was anti-emesis, followed by prophylaxis of peripheral neuropathy, hand–foot syndrome, oral mucositis, pain relief, prevention of constipation, vascular pain, and so on (Fig. 2c). Before April 2008, most of these practices were carried out by physicians and nurses. Therefore, participation of two pharmacists in the oncology team led to a reduction in the workload of other medical staff.

As shown in Fig. 3, the number of patients (Fig. 3a) and the amount of mixing of anticancer injections (Fig. 3b) in the outpatient chemotherapy clinic gradually increased since April 2008. The average of monthly number of patients was significantly higher after involvement of pharmacists in the team than before (128 ± 13 vs. 183 ± 36, mean $\pm$ SD, $P < 0.001$), and annual number of patients increased from 1573 to 2193. Similarly, the amount of mixing of anticancer injections increased by 88% (259 ± 20 vs. 487 ± 109, $P < 0.001$) and ultimately monthly income in the outpatient cancer chemotherapy clinic was significantly ($P < 0.001$) elevated from 10.7 ± 1.8 million yen (111.0 ± 18.9 thousand) to 21.1 ± 5.8 million yen ($ 221.2 $\pm$ 60.5 thousand), and the total revenue increased from 128 to 255 million yen (from $1.42 to $2.84 million; Fig. 3c).

Table 1 Demographics of patients with breast cancer who underwent for the first time the combination chemotherapy of epirubicin and cyclophosphamide (EC) without or with 5-fluorouracil (FEC)

	2007	2008	*P*-values
No. of patients	33	27	
Age	53.7 (26–69)	53.3 (30–75)	0.876*
Body surface area (m^2)	1.53 ± 0.13	1.48 ± 0.14	0.181*
White blood cell ($\times 10^3$ mm^{-3})	5.4 ± 1.8	5.7 ± 1.4	0.482†
Hg (g dL^{-1})	12.4 ± 1.5	12.8 ± 1.2	0.249†
Platelet ($\times 10^6$ mm^{-3})	23.1 ± 6.9	23.2 ± 6.2	0.977†
AST (U L^{-1})	23.4 ± 11.5	24.8 ± 13.9	0.650†
ALT (U L^{-1})	25.5 ± 17.7	19.0 ± 12.2	0.082†
SCr (mg dL^{-1})	0.65 ± 0.24	0.57 ± 0.08	0.069†
Chemotherapy regimen (courses)			
FEC	11 (33.3%)	5 (18.5%)	0.248‡
EC	22 (66.7%)	22 (81.5%)	
Dose of anticancer agents (mg m^{-2} day^{-1})			
Cyclophosphamide	509 ± 51	563 ± 51	<0.001†
Epirubicin	81 ± 9	82 ± 9	0.647†
5-Fluorouracil	499 ± 40	522 ± 34	0.048†

*Mann–Whitney *U*-test.
†*t*-test.
‡Fisher's exact probability test.

Outcome of intervention by pharmacists to prevent CINV in breast cancer patients receiving anthracycline and cyclophosphamide

Pharmacists made proposals to physicians to facilitate the use of anti-emetic drugs for prophylaxis of CINV according to the clinical practice guideline for anti-emesis [8]. Although the premedication for the prophylaxis of acute CINV was carried out in all patients receiving AC chemotherapy before and after intervention (Fig. 4a), the prevalence of premedication for prevention of delayed CINV was lower before intervention than after intervention (43% vs. 96%, $P < 0.01$). Before intervention, a combination of oral granisetron and a dopamine D_2 blocker metoclopramide (on days 2–4) was predominantly prescribed for the prevention of delayed CINV; however, after intervention, oral dexamethasone (4–8 mg on days 2–4) and prochlorperazine (5 mg on days 2–4) were almost exclusively prescribed for prevention of delayed events. In addition, granisetron was prescribed in 86% of patients on days 2–4, while the agent was given to 58% of patients on the same period after intervention ($P < 0.01$). The compliance of overall anti-emetic premedication (5-HT_3 receptor blocker and dexamethasone on day 1, and

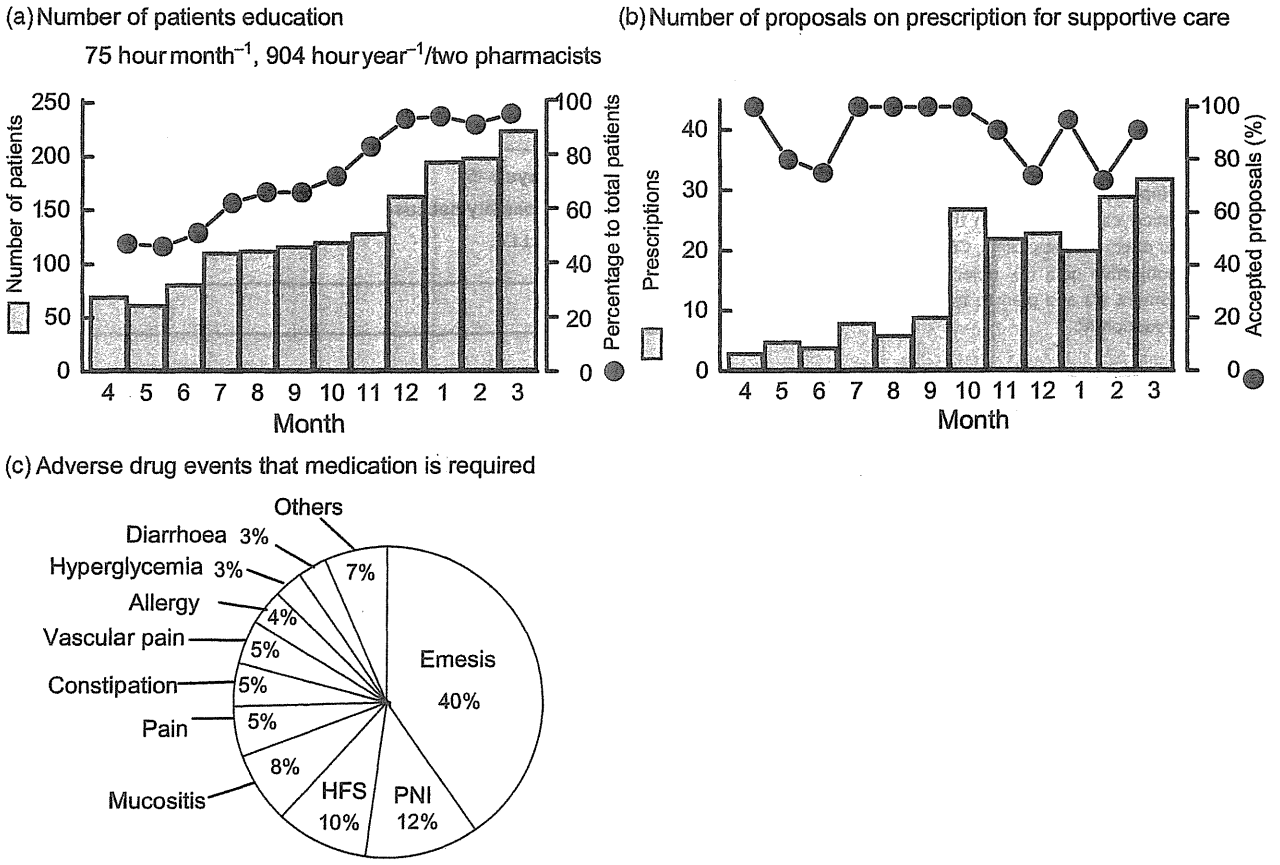

Figure 2 Time course of changes in the performance of pharmaceutical practice in the outpatient cancer chemotherapy clinic (a,b) and the items of supportive care that pharmacists were involved (c). Monthly number of patient education (a), interventions to supportive care (b), and cases that ADRs were prevented (c) were shown. PNI, peripheral neuropathy; HFS, hand-and-foot syndrome.

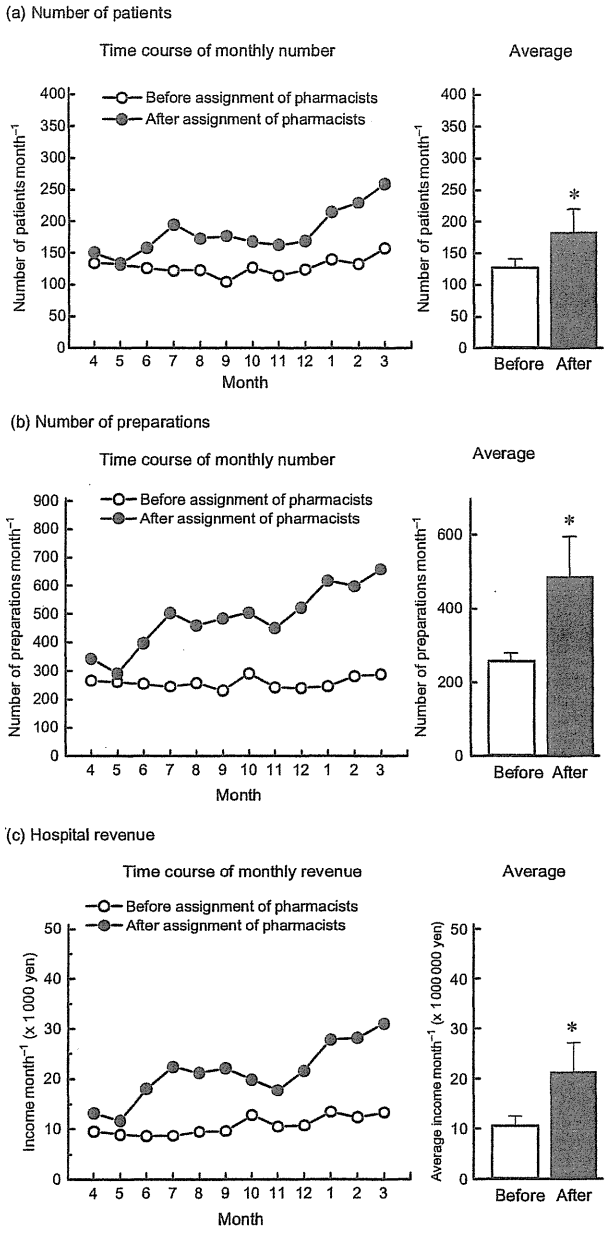

Figure 3 Changes in the number of patients (a), amount of mixing of anticancer injections (b) and hospital incomes (c) in the outpatient cancer chemotherapy clinic after assignment of pharmacists to the cancer chemotherapy clinic. Two pharmacists were involved in the team of outpatient cancer chemotherapy since April 2008. Circles represent the average of monthly data. *$P < 0.01$ by Mann–Whitney *U*-test (a, b) or *t*-test (c).

dexamethasone on days 2–4) was elevated from 43% to 96% ($P < 0.01$). As a consequence, the cost for anti-emesis significantly ($P < 0.01$) decreased by 15.7% from 13 288 ± 2890 yen ($147.7 ± 32.1) to 11 198 ± 3617 yen ($124.5 ± 40.2) after intervention.

The complete response (no nausea and no vomiting) during acute, delayed and overall periods increased, although not significantly, by 13%, 12% and 12%, respectively, after intervention, although the rates of control of vomiting during acute, delayed and overall periods were not different before and after intervention (Fig. 4b).

Discussion

We reported here that pharmacists with experience in oncology shared the workload with physicians and nurses in the outpatient cancer chemotherapy clinic, which led to the increases in the number of patients and hospital revenue, and improvement of supportive care.

The roles of pharmacists in the outpatient cancer chemotherapy clinic were to prepare mixing of anticancer injections, to provide information to patients about cancer chemotherapy and ADRs associated with anticancer drugs, to offer proposals on the prescriptions for supportive care and to provide medical information to physicians and nurses. Instruction to patients by pharmacists was carried out after discussing with physicians and nurses about treatment policy. The average time spent in the instruction to patients was 75 hours month^{-1} and 904 hours in 1 year, most of them were spent by physicians or nurses before assignment of pharmacists, which enabled physicians to treat more patients than before. As a consequence, the number of patients increased every month and the annual number was elevated 1.4-fold as that before assignment of pharmacists, and the annual hospital revenue was almost doubled.

On the other hand, mixing of anticancer injections was carried out by pharmacists using a computer-assisted biohazard safety cabinet developed recently in our hospital [11]. This safety cabinet was fitted with a computer system that works in conjunction with an electronic medical record system, in which the names and amounts (volumes) of anticancer injections that were taken by the pharmacist were checked by the computer system. There have been no mixing errors since introduction (April 2007), indicating that the system contributed largely to the safe management in cancer chemotherapy.

One of important roles of pharmacists in cancer chemotherapy is to prevent or relieve ADRs associated with anticancer drugs. Cancer chemotherapy is often accompanied by a variety of ADRs, including nausea, vomiting, myelosuppression, infectious diseases, oral mucositis, peripheral neuropathy, diarrhoea, dermatitis, acute renal or hepatic failure, congestive heart failure, alopecia, and so on. In our outpatient cancer chemotherapy clinic, the most common item of ADRs that pharmacists were involved was CINV.

According to the clinical practice guidelines for prevention of CINV [7–9], the recommended anti-emetic regimen for AC chemotherapy are a combination of the 5-HT_3 receptor antagonist, dexamethasone and the NK_1 receptor antagonist for the prophylaxis of acute CINV and a concomitant use of dexamethasone and the NK_1 receptor antagonist for the prophylaxis of delayed CINV. In the present survey, most of patients were pretreated with granisetron injection (3 mg) in combination with dexamethasone for prevention of acute events. However, for the prophylaxis of delayed events, granisetron tablet (2 mg) in combination with metoclopramide was predominantly prescribed before intervention by pharmacists. It has been demonstrated that dexamethasone is effective in preventing delayed events of CINV [12,13].

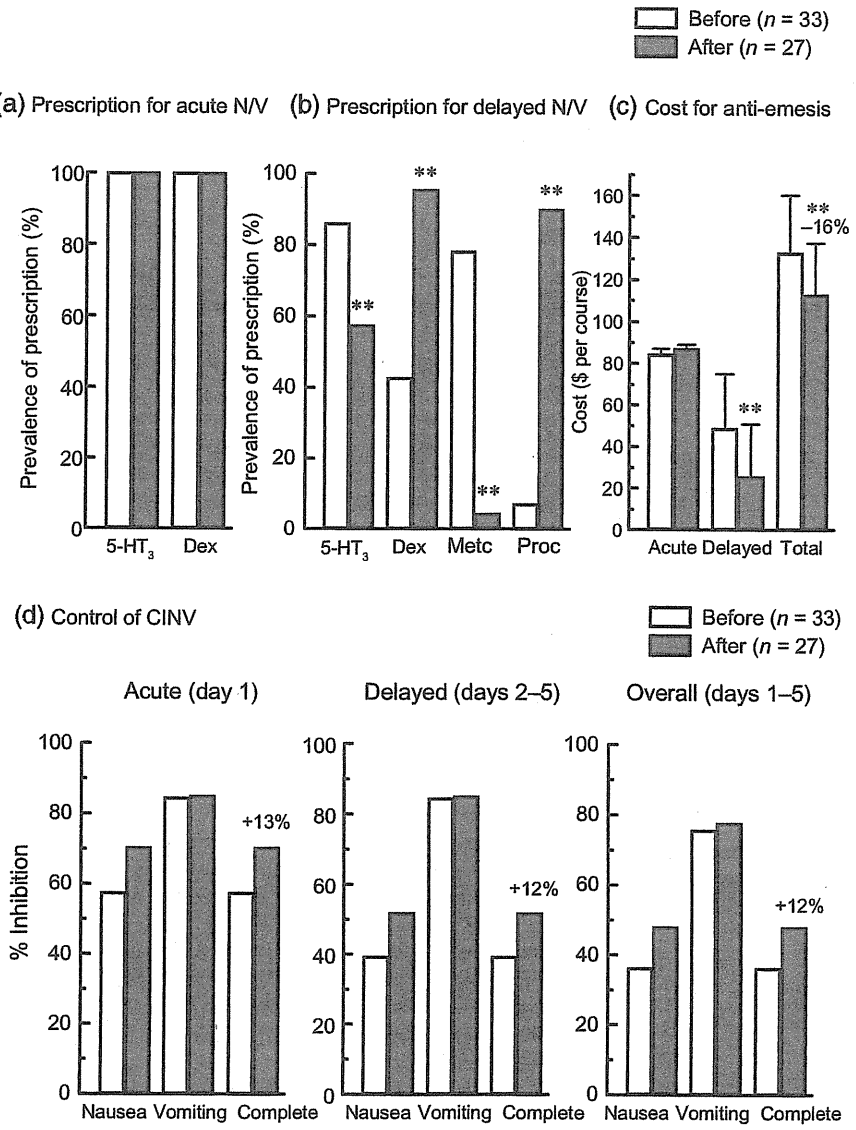

Figure 4 Comparison of prevalence of anti-emetic treatment for prophylaxis of acute (a) and delayed (b) chemotherapy-induced nausea and vomiting (CINV), cost for anti-emetic treatment (c) and control of CINV during acute, delayed and overall periods (d) in breast cancer patients who undertook chemotherapy containing anthracycline and cyclophosphamide before and after assignment of pharmacists. $^{**}P < 0.01$ by Fisher's exact probability test (b), Mann–Whitney *U*-test (c). N/V, nausea and vomiting; Dex, dexamethasone; Metc, metoclopramide; Proc, prochlorperazine.

However, the effect of a 5-HT_3 receptor antagonist on delayed CINV is controversial: Kaizer *et al.* [14] showed in a multi-centre randomized double-blind study consisting of 302 patients that treatment of oral ondansetron after 24 hours is significantly more effective than placebo in prophylaxis of delayed nausea and vomiting. In contrast, Olver *et al.* [15] reported in a multi-centre randomized double-blind study consisting of 640 patients who received cisplatin-containing chemotherapy that oral ondansetron treatment after 24 hours shows only a slight and not significant protective effect against delayed nausea and vomiting compared to placebo (complete inhibition of delayed nausea and vomiting: 54% with ondansetron versus 49% with placebo). On the other hand, the protective effect of a 5-HT_3 receptor antagonist against delayed emesis was not observed in patients who received dexamethasone after 24 hours [16]. A meta-analysis has shown that a 5-HT_3 receptor antagonist is significantly effective in preventing delayed CINV, when compared to placebo, but has no additive effect on delayed CINV, when treated in combination with dexamethasone [17,18]. We also reported that the treatment with granisetron on days 2–4 does not enhance the anti-emetic effect but significantly increases the incidence of constipation in breast cancer patients who took dexamethasone before and after treatment with highly emetogenic chemotherapy [19]. Taken together, pharmacists recommended prescribing dexamethasone tablet (8 mg) instead of granisetron for prevention of delayed events, thus dexamethasone was prescribed on days 2–4 in almost all patients after pharmaceutical intervention. Moreover, it has been demonstrated in patients receiving doxorubicin-containing chemotherapy that oral prochlorperazine (10 mg every 8 hours on days 2 and 3) is more effective in reducing the incidence of delayed nausea than 5-HT_3 receptor antagonists [10]. Therefore, pharmacists recommended the use of prochlorperazine instead of metoclopramide on days 2–4. These changes in prescriptions resulted in saving the medical cost by 16%. The rate of overall complete

response (no nausea and no emesis with no rescue) was elevated from 36% before intervention to 48% after intervention. The rate of overall complete response in patients receiving AC chemotherapy after intervention was generally consistent with those reported earlier: the complete response during 5 days (0–120 hours) following AC chemotherapy is reported to be 42% [20] and 47% [21], in patients receiving ondansetron (8 mg, p.o., on days 1–3) and dexamethasone (20 mg, p.o., on day 1) for anti-emetic treatment. Saito *et al.* [22] reported in Japanese patients receiving AC chemotherapy that the complete response during 0–120 hours is 50%, when granisetron (40 $\mu g\ kg^{-1}$, i.v., on day 1) and dexamethasone (16 mg, i.v., on day 1 and 4 mg, p.o., on days 2 and 3) are treated. By replacing delayed granisetron plus metoclopramide with dexamethasone plus prochlorperazine, the overall complete response increased slightly and not significantly to 48%. Taken together, it is suggested that cost-effective anti-emetic treatment was attained by pharmaceutical intervention.

Although clinical practice guidelines for anti-emesis recommend using neurokinin NK_1 receptor antagonists such as aprepitant for prevention of CINV associated with AC chemotherapy, aprepitant was not used in the present study because of the lack of availability of the compound during the study period. This drug has been introduced in Japanese market in December 2009. Aprepitant used in addition to the conventional anti-emetic regimen (125 mg, p.o., on day 1 and 80 mg, p.o., on days 2 and 3) is reported to increase the rate of complete response by 9–16% [20,21]. Therefore, the present anti-emetic regimen should be upgraded by addition of aprepitant to improve complete response.

In conclusion, two pharmacists including an oncology pharmacy specialist were assigned to the outpatient cancer chemotherapy clinic to contribute to the improvement and enhancement of the quality of medical practices. Pharmacists were in charge of patient education, verification of cancer chemotherapy regimens, monitoring ADRs, proposal of prescriptions for supportive care and provision of medical information to other medical staff. Their activities resulted in an enhancement of therapeutic efficiency in respect of the number of patients and the amount of hospital income. In addition, cost-effective anti-emetic treatment was attained.

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特集　わが国における消化器外科の現況と今後

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吉田　和弘　　山口　和也　　高橋　孝夫

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