Table 2. Review of phase III clinical trials in Japan

	S-1/ S-1 + CPT-11 (GC0301/TOP-002)	S-1/ CPT-11 + CDDP (JCOG 9912)	S-1/ S-1 + CDDP (SPIRITS trial)	S-1/ S-1 + docetaxel (START trial)
MST, months	10.5/12.8	11.4/12.3	11.0/13.0	11.0/13.0
1-year survival rate	45.0%/52.0%	49.7%/52.5%	46.7%/54.1%	46.0%/52.5%
2-year survival rate	22.5%/18.0%	–/–	15.3%/23.6%	20.6%/23.7%

(PR) (total RR 54%). Of the 106 patients with target tumors assigned to receive S-1 alone, 1 showed a CR and 32 showed a PR (total RR 31%). Based on this trial, S-1 plus cisplatin became regarded as a new standard first-line treatment for patients with AGC in Japan.

A randomized phase III trial was conducted to evaluate the efficacy and safety of IRIS (S-1 + CPT-11) versus S-1 alone for AGC. Patients with previously untreated AGC were randomized to arm A (oral S-1, 80 mg/m^2 on days 1–28, every 6 weeks) or arm B (IRIS: oral S-1, 80 mg/m^2 on days 1–21; intravenous CPT-11, 80 mg/m^2 on days 1 and 15, every 5 weeks) by dynamic allocation. As a result, 326 patients were randomized to arm A (162 patients) or arm B (164 patients), with a final 315 evaluable patients (160 in arm A and 155 in arm B). Although the MST of the arm A patients was 318 days (95% CI 286–395) and that of the arm B patients was 389 days (95% CI 324–458), arm B did not show significant superiority to arm A. The RRs were significantly different, being 26.9% in arm A versus 41.5% in arm B in 187 RECIST (Response Evaluation Criteria in Solid Tumors)-evaluable patients. Based on this trial, IRIS achieved MST and was better tolerated; however, it did not show significant superiority to S-1 alone in terms of the overall survival, and could thus not become a first-line treatment for AGC.

A randomized phase III study comparing S-1 alone with the S-1 + docetaxel combination was conducted through the JACCRO GC03 trial. This study was a prospective, multicenter, multinational (Korea and Japan), nonblinded, randomized, phase III study of patients with AGC. Patients were randomly assigned to receive 3-week cycles of treatment arm A (docetaxel and S-1) or 6-week cycles of treatment arm B (S-1 only). The primary objective of the study was to compare the median overall survival of the test arm (docetaxel and S-1) with that of the control arm (S-1 only). The secondary objectives were to assess the time to tumor progression (defined as the time from randomization to the date of first documentation of progressive disease), to determine the clinical response/RR (defined as the sum of the CR and PR according to RECIST criteria) and to evaluate the safety of the 2 regimens. It was expected that 628 patients (314 in each treatment arm) would be enrolled in this trial and this was exceeded, with confirmation of 628 patients from 103 centers in September 2008. Although the primary end point was not met, PR and RR were superior in the combination arm [44]. What is more interesting in this combination is that the docetaxel enhances the cytotoxic effect of 5-FU via biochemical modulations through decreased expression and activity of TS and dihydropyrimidine dehydrogenase and increased activity of orotate phosphoribosyltransferase [41]. It was recently reported that these effects can be modulated even more by molecular targeting agents including mTOR inhibitor [42].

The Role of Surgical Intervention in Stage IV Gastric Cancer Patients

Palliative and Volume Reduction Surgery

Gastric bypass, jejunostomy, ileostomies and colostomies are sometimes performed because of the pyloric stenosis of the primary tumor and/or tumors of the peritoneal disseminated disease of gastric cancer, and often, even if not by R0 resection, primary tumors are removed because of bleeding or obstruction of the stomach and bowels, all of which are regarded as palliative surgery. In the 1980s, the resection of the primary tumors and the removal of metastatic disease were often conducted as tumor volume reduction surgery. However, the prognosis of patients was not satisfactory because although the main treatment tool was palliative chemotherapy, the RR of chemotherapy regimens in those days was 20–30% and in the end, the patients died due to the tumor burden in spite of the reduction surgery. In order to improve the survival of the patients, new regimens or new chemotherapeutic

agents with more effective and reduced adverse effects were called for, but until recently, palliative chemotherapy was regarded as the standard strategy in stage IV or recurrent gastric cancer patients.

Adjuvant Surgery

As described in the previous section, after the new chemotherapeutic agents were developed including S-1, docetaxel, paclitaxel, irinotecan, oxaliplatin and molecular targeting agents, the RR and survival of patients have improved dramatically. Interestingly, it was often reported that with newly developed chemotherapeutic regimens, the tumors were downstaged and the curative resections or R0 resections were performed in stage IV gastric cancer patients [24]. It is only recently that those cases were often found successful after treatment with S-1 + CDDP and S-1 + docetaxel regimens [45]. These operations are called 'adjuvant surgery' as previously reported [24]. The indications for adjuvant surgery are that curative resection (not palliative) can be expected, based on the response to chemotherapy, the absence or CR of other distant metastases such as peritoneal dissemination, extensive lymph node metastases or lung metastasis. The macroscopically complete removal of liver deposits is feasible, and minimal residual tumors after chemotherapy in distant lymph nodes can be extensively removed. Palliative chemotherapy is the standard strategic approach for stage IV gastric cancer. However, if treatment has been successful with CR or PR and the tumors are considered resectable or R0 resection is deemed possible, it could be feasible to perform aggressive operations to remove the residual tumors, although these operations can be regarded as adjuvant. Of course, it might be required to continue chemotherapy after these surgeries, even after R0 resections, because these cases were treated as stage IV gastric cancer. This chemotherapeutic strategy is called perioperative chemotherapy [10]. In other words, so-called neoadjuvant chemotherapy (NAC) was performed, downstaging of the tumors followed, and as a result of this, the R0 resections could take place. It must be clarified that, strictly speaking, NAC is the chemotherapy which is conducted in patients with potentially curative resectable tumors before treatment [46]. NAC is performed in order to improve the prognosis or improve the resectability of the tumors. For aggressive operations in stage IV gastric cancer patients, it can be termed adjuvant surgery with perioperative chemotherapy. The merit of adjuvant surgery in stage IV gastric cancer with a favorable response to chemotherapy is that the compliance with chemotherapy is better before surgery compared to afterwards, and secondly, it can be regarded as an in vivo sensitivity test. Thirdly, tumors definitely acquire resistance to chemotherapy, which is why aggressive operations are preferred while the tumor growth is well controlled with chemotherapy, because it is well known that tumor growth is enhanced by the cytokines after surgical treatment [47]. The best timing for the operation is when the best response of the tumor to chemotherapy is observed, not when the tumor is increasing in size or has acquired the ability to regrow. Generally, we estimate the best timing for the removal of the tumor to be when the CR or PR is detected when 4–6 cycles of S-1 + CDDP or S-1 + docetaxel regimens have been performed. This strategy is regarded as rescue surgery, oncosurgery or conversion therapy (recently conducted in metastatic liver tumors from colorectal cancer) [48–52]. In the REGATTA trial, palliative surgery followed by chemotherapy for stage IV gastric cancer is now being conducted in Japan and Korea in order to evaluate the significant roles of tumor volume reduction and interesting results are expected.

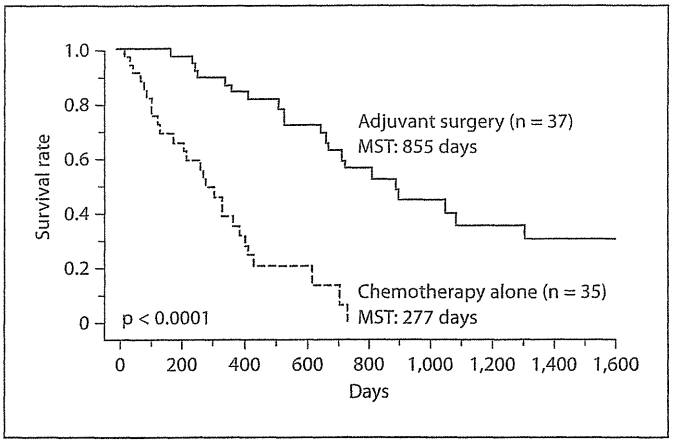

Fig. 5. Survival of the patients with adjuvant surgery in stage IV gastric cancer.

From 2001 to 2009, we treated 158 stage IV gastric cancer patients who had received S-1 + CDDP and S-1 + docetaxel treatment. We performed adjuvant surgery aiming at R0 resection of the primary and metastatic disease on 37 of these patients. The median survival of the patients who underwent surgery was 855 days after the initial start of the chemotherapy, while for those without an operation it was 277 days (fig. 5). As we reported in a preliminary retrospective analysis [24], this type of surgery might be effective in patients diagnosed as stage IV

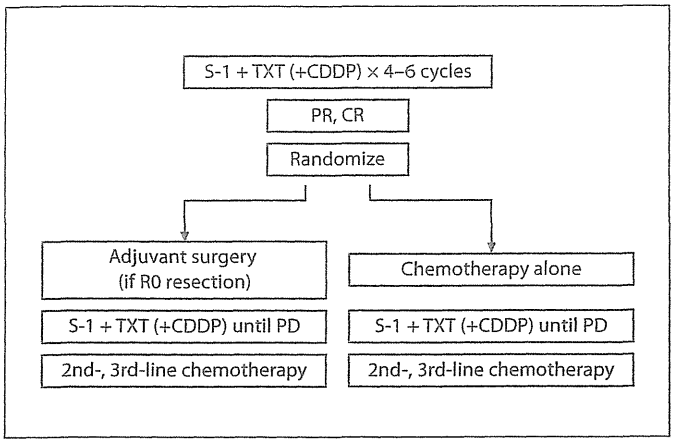

Fig. 6. Future trial of adjuvant surgery. Perioperative chemotherapy in stage IV gastric cancer: a randomized controlled trial of S-1 + docetaxel with or without CDDP. PD = Progressive disease; TXT = docetaxel.

due to liver metastasis or distant lymph node metastasis, but not for cases of peritoneal dissemination. Of course, there is a bias that the adjuvant surgery group had a good response to chemotherapy and the others not. In order to prove the significance of the adjuvant surgery, further analysis will be needed. Under investigation by a randomized phase II/III study, using S-1 + docetaxel and/or CDDP among patients who had had CR or PR and were considered curatively resectable, patients were randomized to a 'continuation of chemotherapy' group or an 'adjuvant surgery followed by chemotherapy (perioperative chemotherapy)' group (fig. 6).

Salvage Surgery

Salvage surgery is regarded as the surgery that is performed after curative radiation or chemoradiation therapy to remove the residual or regrown tumors which have invaded adjacent organs (as described in the Japanese guidelines of esophageal cancer [53, 54]). Salvage surgery is conducted in locally advanced tumors, but adjuvant surgery is conducted in metastatic cancer. Indeed, using the term 'adjuvant' in palliative surgery, even if it is after successful chemotherapy in stage IV gastric cancer, might be criticized. Because, in general, the term 'adjuvant' can be used when the tumor does not exist macroscopically, the term 'adjuvant chemotherapy' is used for chemotherapy when an R0 resection has been performed. In this sense, the term 'adjuvant surgery' could be defined as the curative surgery after CR was detected by chemotherapy in stage IV cancer. Further discussion might be required to determine the most appropriate terminology.

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Docetaxel, Nedaplatin, and S-1 (DGS) Chemotherapy for Advanced Esophageal Carcinoma: A Phase I Dose-escalation Study

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Abstract. *Aim: More effective regimens are urgently needed for treatment of esophageal carcinoma; therefore, we conducted a phase I trial of a combination of docetaxel, nedaplatin, and S-1 (DGS) to determine the optimal dose in patients with advanced esophageal carcinoma. Patients and Methods: We studied 14 patients with previously untreated advanced cervical esophageal carcinoma with T3-4 tumors and/or M1 staging and esophageal carcinoma with cervical lymph node metastasis. The patients received an infusion of docetaxel at different dose levels (levels 1, 2, 3, 4: 25, 30, 35, 40 mg/m^2, respectively) and an infusion of nedaplatin (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. Results: Dose-limiting toxicities (DLTs) included febrile neutropenia and leukopenia. DLTs occurred in 2 out of 5 patients at level 4. The response rate was 78.6 (11/14)%, including a complete response rate of 35.7(5/14)%. Conclusion: The DGS regimen reported here was well tolerated and toxicities were manageable. The maximum tolerated dose was level 4, and the recommended dose was determined to be docetaxel at 35 mg/m^2 with nedaplatin at 40 mg/m^2 plus S1 at 80 mg/m^2. We found that our regimen, administered on an outpatient basis, showed high activity and tolerance. A phase II study has been started.*

Locally advanced or widespread metastatic esophageal carcinoma is difficult to treat and is often thought to progress rapidly. Quick deterioration of respiratory and nutritional states makes outpatient care impossible and leads to an extremely poor prognosis. It is necessary to establish effective and safe outpatient chemotherapy that provides survival benefits and improvements in quality of life compared with best supportive care.

Over the past several decades, patients with unresectable or inoperable esophageal disease have usually been treated with various chemotherapy strategies, and prognosis is extremely poor, with a mean survival time of less than 8.1 months with current chemotherapies used singly or in combination with 5-fluorouracil (5-FU), vindesine, mitomycin, docetaxel, paclitaxel, cisplatin, irinotecan, vinorelbine, or capecitabine (1-3).

Standard chemotherapy is fluorouracil and cisplatin combination therapy (FP), for which the median survival time is reported to be 9.2 months for responders and 5.3 months for nonresponders (4, 5). The response rates reported with FP range from 35 to 40%, whereas two-year survival rates of patients with locally advanced esophageal cancer range from 8 to 55% (mean 27%) (6-8).

To improve both local and distant tumor control in patients with esophageal carcinoma, new therapeutic combinations must be developed. Recently, favorable antitumor effects of combination therapy with fluorouracil and taxanes were reported. Many studies have shown that taxanes have significant activity in patients with locally advanced and metastatic esophageal carcinomas (9). For advanced esophageal carcinoma, a combination of docetaxel and 5-FU with concurrent radiotherapy had good efficacy (10).

Docetaxel, cisplatin, and 5-FU (DCF) have exhibited different mechanisms of activity in upper gastrointestinal malignancies. In a randomized phase III study from the V325 study group, advanced gastric or gastroesophageal junction cancer patients receiving DCF not only had statistically significantly improved overall survival and time to tumor progression, but they also had better preserved quality of life compared with patients receiving FP therapy (11, 12).

We previously reported a phase I study of DCF for advanced esophageal squamous cell carcinoma. To minimize toxicity and maximize dose intensity, we investigated a

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Key Words: Chemotherapy, docetaxel, nedaplatin, S1, esophageal carcinoma, phase I.

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biweekly regimen. This regimen was tolerable and highly active. The response rate was 88.9%, including a complete response rate of 33.3% (13). However, hospitalization is necessary with this regimen, and cisplatin requires hydration and is thus not easily used if renal dysfunction is present.

The combination of docetaxel and S1 is highly active and well tolerated for advanced or recurrent gastric cancer (14), and synergy of this combination has been reported *in vitro* (15). S1 (TS1®; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) was developed by the biochemical modulation of tegafur, a 5-FU prodrug; gimeracil, a dihydropyrimidine dehydrogenase inhibitor; and oteracil, which inhibits pyrimidine phosphoribosyl transferase specifically in the gastrointestinal tract and thereby reduces the phosphorylation of 5-FU in the intestine. S1 is a well-designed oral formulation, with the dual actions of reinforcing antitumor activity and reducing gastrointestinal toxicity (16).

In a late phase II study of nedaplatin (*cis*-diammineglycolatoplatinum) in patients with advanced head and neck cancer, the response rate was 37.5%, higher than that reported for cisplatin, and carboplatin (17-19). Nedaplatin is a less nephrotoxic analogue of cisplatin. Drug secretion and re-absorption in the convoluted tubules are not seen, and it is less toxic to the gastrointestinal tract mucosa than is cisplatin, which is a second-generation platinum derivative that has demonstrated potent antitumor activity against lung, testicular, esophageal, gynecological, and head and neck cancers. Platinum primarily acts as an alkylating agent, whereas docetaxel stabilizes microtubules and inhibits mitosis; therefore, a combination of docetaxel and platinum should be expected to result in additive antitumor effects and non-overlapping toxicity profiles.

A phase II study of induction chemotherapy with docetaxel and nedaplatin for oral squamous cell carcinoma showed a good response rate of 33.3% (20). Hydration is not required before or after nedaplatin administration, thus allowing use of the drug on an outpatient basis.

We therefore conducted a phase I clinical trial of the triplet combination of docetaxel, nedaplatin, and S-1 (DGS) in patients with advanced cervical esophageal carcinoma with T3-4 tumors and/or M1 staging and esophageal carcinoma with cervical lymph node metastasis. The goal of this trial was to determine the recommended dose (RD) for use in phase II trials on the basis of the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). Secondary objectives were treatment-related toxicity and efficacy.

Patients and Methods

Patient eligibility criteria. Patients eligible for the present study had to be ≥20 years of age at the time of registration and have histologically or cytologically confirmed squamous cell carcinoma (SCC) or either T3/T4 or recurrent adenocarcinoma. An Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 was required, as were a life expectancy of >12 weeks and adequate liver, bone marrow, renal, and cardiovascular function as evidenced by the following measures: serum bilirubin ≤1.5 mg/dl, neutrophil count ≥1,500/mm^3, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of less than or equal to twice the upper limit of normal range, platelet count ≥100,000/mm^3, hemoglobin ≥8.0 g/dl, and serum creatinine ≤1.5 mg/dl or creatinine clearance rate >60 ml/min. In addition, the latest chemotherapy treatment must have been at least 4 weeks before trial enrollment. Major exclusion criteria included the following: previous treatment with taxane therapy for recurrent disease or irradiation to major bone areas; serious concomitant malignancy; active infectious disease with fever; severe drug allergy; symptomatic peripheral neuropathy; uncontrolled diabetes mellitus, hypertension, angina pectoris, arrhythmia or congestive heart failure; and interstitial pneumonia or lung fibrosis. Prior to study entry, all patients were required to sign an informed consent form approved by the Ethical Committee of Gifu University Hospital. Ultimately, 14 patients were enrolled in the study, and all fully underwent DGS therapy.

Study design. The primary objectives of this phase I dose-escalation study were to determine the MTD and toxicity of escalating doses of docetaxel combined with a fixed dose of nedaplatin and S-1 in patients with advanced esophageal carcinoma. The secondary objective of the study was to obtain preliminary data regarding clinical response. This study of DGS was conducted at the Department of Surgical Oncology, Gifu University School of Medicine.

At least three patients were entered at each docetaxel dose level. No dose escalation for individual patients or within a dose level was permitted. All three patients at a given dose level had to complete the first two cycles of treatment without DLT before further patients were enrolled in the next dose level. If DLT did not occur, the next dose level was explored. Doses were increased in sequential groups of three patients until the MTD was established or the highest intended dose levels were reached. If any of the three patients experienced DLT, an additional three patients were treated at the same dose level. If more than three out of the six patients at a given dose level experienced DLT, that dose level was defined as the MTD. The dose level one step below the MTD was set as the RD for further evaluation in a phase II study.

Treatment plan. The patients received an intravenous infusion of docetaxel at different dose levels (level 1, 25 mg/m^2; level 2, 30 mg/m^2; level 3, 35 mg/m^2; and level 4, 40 mg/m^2) and an intravenous infusion of nedaplatin (40 mg/m^2) followed by 500 ml hydration on day 8 plus oral administration of S1 (80 mg/m^2/day) twice daily (within 30 minutes after the morning and evening meals) for two consecutive weeks at two-week intervals (one cycle).

On day 8, patients received docetaxel diluted in 250 ml of normal saline at the assigned dose. It was infused intravenously over 2 hours. Then nedaplatin was prepared in normal saline at a dose of 40 mg/m^2 and administered intravenously over 2 hours followed by 500 ml hydration. If the patient had upper digestive tract obstruction, S-1 was administered through a 6-8 Fr nasogastric tube inserted in the stomach. The dose-escalation scheme is described in Table I. The initial dose of docetaxel was 25 mg/m^2 (dose level 1), and this was increased up to a maximum of 40 mg/m^2 in 5-mg/m^2 steps.

Table I. *Dose-escalation scheme.*

Dose level	Docetaxel (mg/m^2)	Nedaplatin (mg/m^2)	S1 (mg/m^2)
1	25	40	80
2	30	40	80
3	35	40	80
4	40	40	80

Supportive therapy for treatment and prophylaxis for expected side-effects were administered. All patients were premedicated with intravenous administration of 2 mg of granisetron. Hypersensitivity reactions were treated with prophylactic use of intravenous dexamethasone at 8 mg, which was infused 1 hour prior to the administration of docetaxel. Further dexamethasone was prescribed at a dose of 8 mg orally for 2 days after administration of docetaxel to reduce the risk of hypersensitivity reaction and fluid retention. Diuretics were added at the discretion of the treating physician. Additional antiemetics were recommended on subsequent days as needed.

Granulocyte colony-stimulating factor (G-CSF) was administered once a day if the neutrophil count was below 500/μl or if febrile neutropenia (fever ≥38°C and neutrophil count of <1,000/μl) were observed. G-CSF was stopped if the neutrophil count was >5,000/μl. To avoid severe mucositis, L-glutamine at 8 g was administered orally to all patients.

Patient monitoring and response criteria. Complete staging procedures for documentation of disease extent, which included assessment of ECOG performance status, medical history, and physical examination, were performed on all patients. Laboratory evaluations were obtained within one week before initiation of treatment and at the start of each treatment cycle and included the following: complete blood cell count; serum electrolytes; urea; creatinine and 24-hour creatinine clearance; bilirubin; alkaline phosphatase and transaminases; carcinoembryonic antigen (CEA), squamous cell carcinoma-related antigen (SCC), carbohydrate antigen 19-9 (CA19-9) and cytokeratin 19 fragment (CYFRA) measurements, and electrocardiogram. For baseline reference, either computed tomography (CT) or magnetic resonance imaging (MRI) and positron-emission tomography CT were performed within two weeks prior to study entry. During chemotherapy, a complete blood count was measured in all patients every week, and levels of electrolytes, serum creatinine, transaminases, alkaline phosphatase and bilirubin, and plasma urea were measured every two weeks. We used the Common Terminology Criteria for Adverse Events (v3.0) to grade the medical history, which included physical examination and toxicity assessment, every two weeks during the study. Tumor measurements were made from radiographic films or scans taken to document treatment response during therapy and were repeated at every second cycle of treatment or sooner if the patient appeared to show disease progression. We assessed tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (21). A barium meal study, endoscopy, ultrasonography, and CT or MRI was used to evaluate the response status of measurable lesions.

We defined complete response as complete disappearance of all clinically detectable malignant disease and partial response as a ≥30% decrease in the sum of the perpendicular diameters of all measurable lesions present for at least 4 weeks. We defined progressive disease as either a ≥20% increase in the sum of the products of measurable lesions over the smallest sum observed or as the appearance of new lesions. Stable disease did not qualify as complete response, partial response, or progressive disease.

Table II. *Characteristics of patients.*

Characteristic	
No. of patients	14
Age, years	
Median	65.9
Range	40-81
Gender	
Male	11
Female	3
Performance status	
0-1	14
Histology	
SCC	11
Adenocarcinoma	3
Disease status	
Locally advanced	7
Locally advanced and metastatic	7
Stage of disease	
T3N1M0	2
T3N2M0	2
T4N3M0	3
T3N4M1	4
T4N1M1	1
T4N2M1	2
Site of primary disease	
Ut	3
Mt	6
Lt	5
Differentiation	
Well differentiated	3
Moderately differentiated	5
Poorly differentiated	6

SCC: Squamous cell carcinoma; Ut: upper lesion of thorasic esophagus; Mt: middle lesion of thorasic esophagus; Lt: lower lesion of thoracic esophagus.

Definition of DLT and criteria for dose modifications. The Common Terminology Criteria for Adverse Events (v3.0) was used to evaluate and score toxicity. We defined DLT to include the following: febrile grade 3 neutropenia, grade 4 neutropenia lasting >7 days, grade 3 leucopenia, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding tendency, or any grade 3 or 4 non-hematological toxicity other than nausea/vomiting, anorexia, diarrhea, alopecia, and general fatigue. Occurrence of hematological toxicity of ≥grade 3 resulted in delay of therapy until the platelet count was at least 100,000/mm^3 and absolute neutrophils were ≥2,000/μl. Occurrence of gastrointestinal toxicity of ≥grade 3 resulted in delay of chemotherapy until the optimum dose could be tolerated. Treatment was repeated every 4 weeks or as soon as the patient had recovered from the toxicity of the previous chemotherapy. However, the patient was removed from the study if toxicity persisted for more than two weeks following the time of planned treatment. Delay in

Table III. *Dose-escalation scheme in relation to dose-limiting toxicity and response.*

Dose level of docetaxel	Patients	No. of cycles	DLT	Type	Response
25 mg/m^2	3	24	0	–	2 CR, 1 SD
30 mg/m^2	3	15	0	–	1 CR, 2 PR
35 mg/m^2	3	16	0	–	2PR, 1 SD
40 mg/m^2	5	17	4	2 Leucopenia 2 Febrile neutropenia	2 CR, 2 PR, 1 SD
Total	14	72	4		Response rate: 78.6%

DLT: Dose-limiting toxicity; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

administration of the second cycle of therapy of longer than two weeks was also considered a DLT. Dose modifications for the next dose were based on the most severe toxicity observed since the previous treatment course. If DLT occurred, treatment was interrupted until toxicity resolved to ≤grade 1.

Results

Patient characteristics. Between November, 2008, and January, 2010, 14 patients were enrolled in the present study. Demographic and clinical characteristics of the study population are summarized in Table II. Four docetaxel dose levels were evaluated. A total of 72 courses of chemotherapy were administered, with the median number of courses administered per patient being 5.1 (range, 2-10). All patients had locally advanced esophageal carcinoma or metastatic lesions. Median patient age was 65.9 years (range, 40-81 years). All patients had an ECOG performance status of 0-1. Histology showed well-differentiated carcinoma in 21.4% of the patients and poorly differentiated carcinoma in 42.9%. Only two patients were hospitalized and administered S-1 by nasogastric tube until finishing their second courses. After the second course, S-1 was administered orally to these two patients in the outpatient setting. The other 12 patients were treated solely as outpatients.

Toxicity and dose-finding study. Data on the dose-escalation scheme, DLT, and response are summarized in Table III. Only ≥grade 2 toxicity data were collected and reported, and especially for neutropenia and leucopenia, only ≥grade 3 toxicity data were reported. Patient characteristics were well balanced across all dose levels. No treatment-related deaths were observed.

The level 1 dose (docetaxel 25 mg/m^2) was initially administered to three patients. No patient had grade 3-4 neutropenia lasting five days with fever. Of the three patients treated at dose level 1, all had grade 2 anorexia, one had grade 2 fatigue, and one had grade 2 nausea. Twenty-four courses of chemotherapy were evaluated, and two responders were observed.

Three patients were initially enrolled at dose level 2 (docetaxel 30 mg/m^2). One patient had grade 2 anemia. One patient experienced grade 2 nausea, three experienced grade 2 anorexia, and one patient experienced grade 2 hypersensitivity reaction. Fifteen courses of chemotherapy were administered at dose level 2. All three patients were responders.

At dose level 3 (docetaxel 35 mg/m^2), no patients developed grade 3/4 hematologic toxicity. One patient experienced grade 2 anemia, and one patient had grade 2 thrombocytopenia. Two patients experienced grade 2 anorexia, one experienced grade 1 nausea, one had grade 1 mucositis, and one had grade 1 pericardial effusion. Sixteen courses of chemotherapy were evaluated, and two responders were observed.

At dose level 4 (docetaxel 40 mg/m^2), one out of two patients developed grade 3 toxicity characterized by febrile neutropenia lasting five days with fever, so three patients were added to the cohort at this dose level. Of the five patients treated at this dose level, two had grade 3 leucopenia, two had grade 3 febrile neutropenia lasting five days with fever, one experienced grade 2 nausea, one experienced grade 2 anorexia, and one had grade 2 mucositis. The febrile neutropenia of the two patients was resolved within five days by G-CSF support. Seventeen courses of chemotherapy were evaluated. Among the five patients entered at this dose level, four responders were observed. This dose (docetaxel 40 mg/m^2) was considered the MTD; therefore, the dose of docetaxel for further phase II studies was determined to be 35 mg/m^2.

The frequency of treatment-related toxicities is summarized in Table IV. Grade 3 leucopenia occurred in 2 out of 14 patients, and grade 3 febrile neutropenia also occurred in 2 out of 14 patients (14.3%). Alopecia was the most frequent non-hematologic toxicity with an incidence of 13/14 of patients, followed by anorexia (9/14) and nausea (4/14). Edema (3/14) and hypersensitivity reaction (1/14), which are known toxicities attributed to docetaxel, were observed, but these side-effects were manageable and reversible. Grade 1/2 mucositis occurred in 2 out of 14

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 2)	1 (grade 1) 2 (grade 2)	2 (grade 1) 1 (grade 2)	2 (grade 1) 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

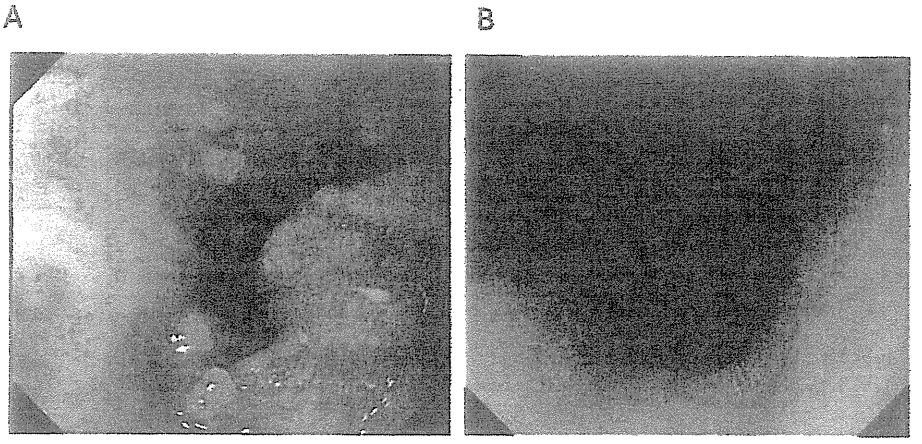

Figure 1. *Endoscopic findings showing an invasive, ulcerative-type cervical esophageal tumor before treatment (A); After chemotherapy (B).*

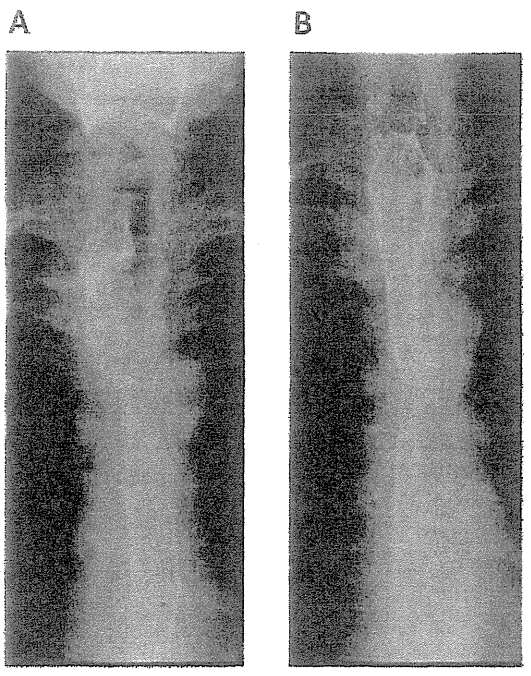

Figure 2. *Esophagographic findings showing circumferential stricture (longest diameter, 55.5 mm) before treatment (A) and after chemotherapy (B).*

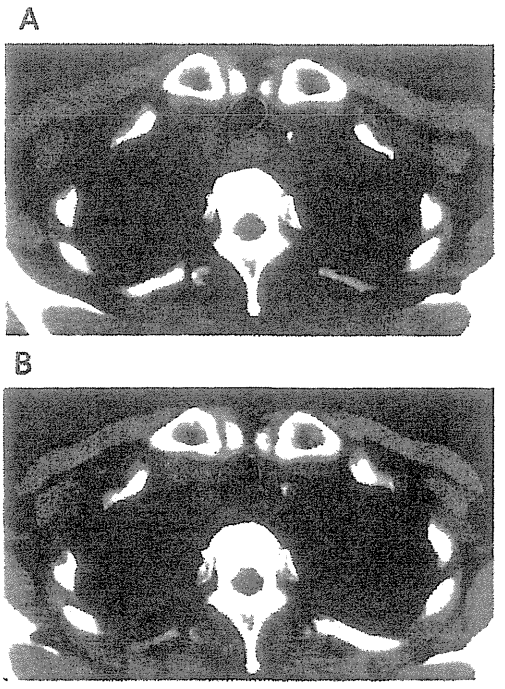

Figure 3. *A: Invasion of the bronchus by tumor was suspected on computed tomography (CT) before treatment. B: After chemotherapy.*

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.

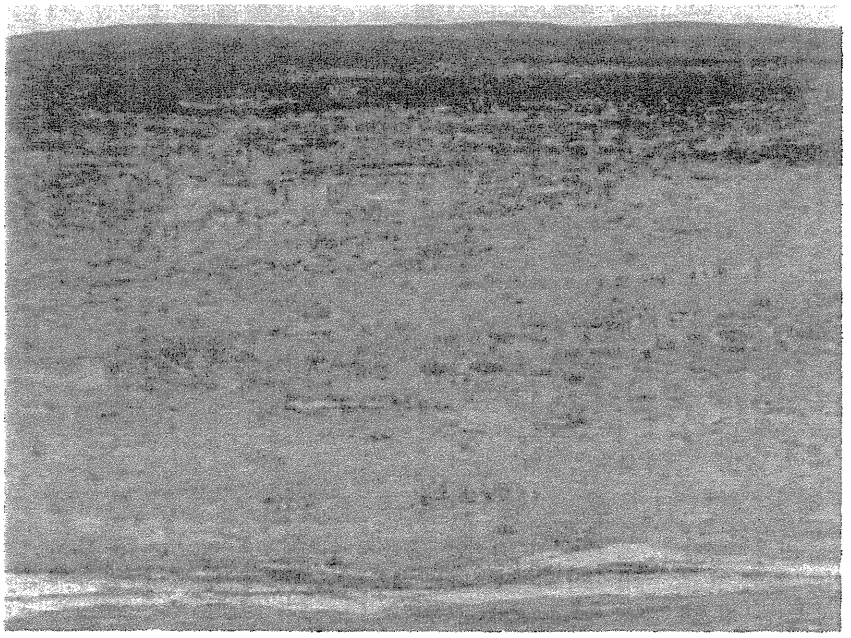

Figure 4. *Histophathological examination of the resected specimen showed an excellent response to the pre-operative chemotherapy.*

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.

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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

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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