Phase II trial of neoadjuvant chemotherapy with docetaxel, nedaplatin, and S1 for advanced esophageal squamous cell carcinoma

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Although standard chemotherapy for esophageal cancer patients is fluorouracil and cisplatin, the prognosis is still unsatisfactory. A new therapeutic regimen combining docetaxel, cisplatin, and 5-fluorouracil was recently developed to improve both local and distant tumor control. We developed a new regimen of docetaxel, nedaplatin, and S1 (DGS) and previously reported the recommended dose in a phase I dose-escalation study. We then undertook a phase II study of DGS for advanced esophageal squamous cell carcinoma. Patients with clinical stage IB/II/III disease were eligible. Patients received two courses of chemotherapy: docetaxel 35 mg/m^2 with nedaplatin 40 mg/m^2 on day 8, 80 mg/m^2 S1 on days 1–14, and 2 weeks off. After completion of chemotherapy, patients underwent esophagectomy. The primary endpoint was the completion rate of protocol treatment (completion of two courses of preoperative chemotherapy and R0 surgery [no residual tumor]). We enrolled 32 patients. The completion rate of protocol treatment was 96.9%. During chemotherapy, the most common grade 3 or 4 toxicity was neutropenia (25.0%). No treatment-related deaths were observed, and the incidence of operative morbidity was tolerable. The overall response rate after chemotherapy was 83.3%. This DGS regimen was well tolerated and highly active. This trial is registered with the University Hospital Medical Information Network (UMIN ID: 000014626).

Esophageal carcinoma is one of the most common malignancies in Japan. Despite improvements in the early diagnosis of esophageal cancer, disease tends to be widespread in most patients at the time of diagnosis.[1] Advanced esophageal carcinoma is difficult to treat and often progresses rapidly. Quick deterioration of nutritional status can make outpatient care impossible and leads to an extremely poor prognosis. Locally advanced esophageal carcinomas are treated with current methods for early diagnosis and perioperative multimodalities. Although morbidity and mortality rates after surgical treatment for advanced esophageal cancer have decreased, the 5-year survival rate after curative surgery is still only 20–36%.[2] Current evidence supports the use of preoperative chemotherapy in patients with operable esophageal cancer,[3,4] but optimal chemotherapy for this disease remains to be defined.

To overcome this unsatisfactory rate of survival, many chemotherapy regimens for locally advanced tumors have been reported to date. In spite of the availability of these varied regimens, the prognosis of advanced esophageal cancer continues to be very poor. Current chemotherapies used singly or in combination with 5-fluorouracil (5-FU), vindesine, mitomycin, docetaxel (TXT), paclitaxel, cisplatin (CDDP), irinotecan, vinorelbine, or capecitabine continue to result in a mean survival time of <8.1 months.[5] For combination therapy with 5-FU and CDDP (FP), which is regarded as the standard, the median survival time is 9.2 months for responders and 5.3 months for non-responders.[6] Rates of response for FP range from 35% to 40%, whereas 2-year survival rates for patients with locally advanced esophageal cancer range from 8% to 55% (mean, 27%).[7–9]

The next generation of regimens for the treatment of both locally advanced and distant metastasis of cancer is currently under development. Several studies have shown significant activity with the taxanes in patients with locally advanced and metastatic esophageal carcinomas.[10–14]

High activity of the combination of TXT, CDDP, and 5-FU (DCF) has been shown for upper gastrointestinal malignancies caused by different mechanisms. For patients with advanced gastric or gastroesophageal junction cancer receiving DCF, the V325 study group reported a statistical improvement in the rate of overall survival (OS) and time-to-tumor progression and better preservation of quality of life compared with patients receiving FP therapy.[15]

Such a triple-combination regimen might also be of benefit in advanced esophageal cancer. But for patients treated with DCF, there is a need for admission and hydration. Clearly, the creation of effective and safe triple-combination regimens, such as those with taxane, platinum, and 5-FU, in an outpatient setting that provide improvements in the quality of life is urgently needed. Hydration is not required for nedaplatin

treatment, and S1 is given orally, thus allowing the use of these drugs on an outpatient basis.

Nedaplatin (*cis*-diamine-glycolate platinum, CDGP) is a less nephrotoxic analogue of CDDP, a second-generation platinum derivative that has shown potent antitumor activity against lung, testicular, esophageal, gynecological, and head and neck cancers. There is no complete cross-resistance between CDDP and CDGP.[16] Drug secretion and re-absorption in the convoluted tubules are not seen with CDGP, and it has low gastrointestinal toxicity when being used with other chemotherapy drugs.[17] Platinum primarily acts as an alkylating agent, whereas TXT stabilizes microtubules and inhibits mitosis; therefore, a combination of TXT and platinum should be expected to result in additive antitumor effects and non-overlapping toxicity profiles. Recently, a phase II study of induction chemotherapy with TXT and CDGP for oral squamous cell carcinoma (SCC) showed a good response rate of 33.3%.[18] Paclitaxel and CDGP have also shown promising response rates of 41.7–43.6% against advanced esophageal cancer.[19]

The combination of TXT and S1 (TS1; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is highly active and well tolerated for advanced or recurrent gastric cancer,[11] and the synergy of this combination has been reported *in vitro*.[12] S1 was developed by the biochemical modulation of tegafur, a 5-FU prodrug, gimeracil, a dihydropyrimidine dehydrogenase inhibitor and oteracil, which inhibits pyrimidine phosphoribosyltransferase 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.[20] Both CDDP and S1 showed safety advantages compared with CDDP/5-FU in advanced gastric or gastroesophageal adenocarcinoma.[20]

Thus, we initially conducted a phase I clinical trial of TXT, CDGP, and S1 (DGS) in patients with advanced esophageal SCC with T3–4 tumors and/or M1 staging for which we determined the recommended dose for use in phase II trials to be TXT 35 mg/m², CDGP 40 mg/m², and S1 80 mg/m².[21] In particular, preoperative chemotherapy for advanced esophageal carcinoma requires tolerability because subsequent radical surgery for esophageal cancer is invasive for patients. We then carried out a phase II single-center study of preoperative chemotherapy with DGS in patients with advanced cervical esophageal SCC with T2–3 tumors and thoracic esophageal carcinoma with cervical lymph node metastasis of clinical stage IB/II/III.

Patients and Methods

Patient eligibility. Eligibility criteria for inclusion in this study included patient age of at least 18 years at the time of enrolment and the presence of histologically or cytologically confirmed SCC, which was locally advanced to clinical stage IB/II/III (International Union Against Cancer TNM classification system, 7th edition).[22] Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a life expectancy of >12 weeks, and adequate liver, bone marrow, renal, and cardiovascular function based on the following values: serum bilirubin ≤1.5 mg/dL, neutrophil count ≥1500/mm³, serum aspartate aminotransferase and alanine aminotransferase ≤twice the upper limit of normal range, platelet count ≥10 × 10⁴/mm³, hemoglobin ≥8.0 g/dL, and creatinine ≤1.2 mg/dL (or creatinine clearance >60 mL/min). We excluded patients treated previously with chemotherapy for

disease or who received irradiation to major bone areas. Other major exclusion criteria were serious concomitant illness, symptomatic infectious disease, severe drug allergy, symptomatic peripheral neuropathy, or uncontrolled diabetes mellitus. Before entry into the study, all participants were required to sign an informed consent form approved by the Ethical Committee of Gifu University Hospital (Gifu, Japan).

Treatment plan. The patients underwent i.v. infusion of both TXT at a dose of 35 mg/m² and CDGP at a dose of 40 mg/m² followed by 500 mL hydration on day 8 plus oral administration of S1 at a twice-daily dose of 80 mg/m²/day (within 30 min of morning and evening meals) for two consecutive weeks at 2-week intervals (one cycle).

On day 8, patients received the assigned dose of TXT diluted in 250 mL normal saline, which was given i.v. over 2 h. Nedaplatin was diluted in normal saline at a dose of 40 mg/m² and then given i.v. over 2 h followed by 500 mL hydration. S1 was administered through a 6–8-Fr nasogastric tube inserted in the stomach if the patient had upper digestive tract obstruction. All patients were premedicated with 2 mg granisetron i.v. To handle hypersensitivity reactions, i.v. dexamethasone at 8 mg was infused prophylactically 1 h prior to TXT treatment. Additional dexamethasone was given orally at a dose of 8 mg for 2 days after TXT to reduce the risk of late emesis. Diuretics were given at the discretion of the treating physician. Additional antiemetics were given on subsequent days as necessary. Two courses of chemotherapy were scheduled in all patients before surgery. After the pre-study evaluation, assigned patients received the first course of chemotherapy in an outpatient setting. Patients with dysphagia of solid meals due to esophageal stenosis received nutritional management through a nasogastric tube from 1 week before the first course of chemotherapy at admission until they could sufficiently ingest a solid meal.

Granulocyte colony-stimulating factor (G-CSF) was given once a day if the neutrophil count was below 500/μL or if febrile neutropenia (fever ≥38°C and neutrophil count <1000/μL) was observed. The G-CSF was stopped if the neutrophil count was >5000/μL. The protocol did not allow the use of prophylactic G-CSF and antimicrobial therapy during chemotherapy.

Treatment assessment and dose modifications. Complete staging procedures were undertaken on all patients to document disease extent, including ECOG performance status, medical history, and physical examination. Clinicopathological factors were analyzed on the basis of the TNM classification.[22]

Pre-study laboratory evaluation included a complete blood cell count, measurement of serum electrolytes, urea, creatinine and 24-h creatinine clearance, bilirubin, alkaline phosphatase and transaminases, carcinoembryonic antigen, SCC, serum carbohydrate-associated antigen, and cytokeratin 19 fragment. An electrocardiogram was obtained within 1 week before initiation of treatment and at the beginning of each treatment cycle. Computed tomography or MRI scans were carried out for baseline evaluation within 4 weeks prior to study entry. A complete blood count was measured in all patients every week during chemotherapy, as were levels of electrolytes, serum creatinine, transaminases, alkaline phosphatase and bilirubin, and plasma urea until the patients underwent surgery.

Toxicity was graded each week during the study in accord with the US National Cancer Institute–Common Terminology Criteria for Adverse Events version 4.0.[23]

Except for the primary tumor, measurable lesions were evaluated with computed tomography or MRI and were assessed in accordance with the Response Evaluation Criteria in Solid

Tumors criteria version 1.0.[24] A complete response was defined as complete disappearance of all clinically detectable malignant disease. A partial response was defined as a ≥30% decrease in the sum of the perpendicular diameters of all measurable lesions lasting at least 4 weeks. Progressive disease was defined as a ≥20% increase in the sum of the products of measurable lesions over the smallest sum observed, or the appearance of new lesions. Stable disease did not qualify as a complete response, partial response, or progressive disease. Patients were closely followed using both endoscopy and radiographic films or scans taken to document treatment response during therapy. Follow-up was repeated during the fourth week of every course of treatment and at 4 weeks after completion of the two courses or sooner if the patient appeared to show disease progression.

Response rate (complete or partial) was confirmed 4 weeks after completion of the two courses of chemotherapy. Then, the patients underwent right thoracotomy with thoracic esophagectomy. Thoracoscopic surgery was also permitted. If disease progression or a new metastasis was detected after the first course, the subsequent cycle was not permitted, and immediate surgery or chemoradiation was mandated. Regional lymphadenectomy consisted of two- or three-field extended lymphadenectomy. Evaluation of residual tumor (R) was classified as follows: R0, no residual tumor; R1, suspicion of residual tumor or microscopic residual tumor; or R2, macroscopic residual tumor.

After surgery, the primary tumor was examined for histopathological changes using the Japanese Classification of Esophageal Carcinoma grading system,[25] with the grades as follows: grade 3, markedly effective, no viable cancer cells, pathologically complete response; grade 2, moderately effective, viable cancer cells account for <1/3 of tumor tissue, whereas other cancer cells show severe degeneration or necrosis; and grade 1, slightly effective, where apparently viable cancer cells account for ≥1/3 of the tumor tissue, but there is some evidence of degeneration of cancer tissue or cells. Grade 1 lesions were further subclassified into grade 1a, viable cancer cells account for ≥2/3 of tumor tissue; grade 1b, viable cancer cells account for ≥1/3, but <2/3, of tumor tissue; and grade 0, ineffective, denoting no discernible therapeutic effect on cancer tissue or cells.

Doses of TXT, CDGP, and S1 were reduced by 20% in the subsequent course if grade 4 hematological toxicity or grade 3 or 4 non-hematological toxicity was present. We postponed the chemotherapy if there was no improvement of grade 3/4 toxicity on the start day of the predetermined course. The protocol treatment was terminated if serious adverse reactions appeared, clear progression of the disease was observed, or the physician otherwise judged that treatment should be stopped.

End-points and statistical methods. The primary objective of this phase II study was compliance with treatment completion. Patients were considered to have completed treatment if they received two courses of chemotherapy and had pathologically proven complete resection (R0). Patients who needed more than two extra weeks from the beginning of the first course of chemotherapy until surgery due to adverse events were not determined to have completed treatment. Secondary objectives included the safety and tolerability of this chemotherapy; evaluation of operative morbidity and mortality; and evaluation of efficacy including response rate, pathological response, 1-year relapse-free survival (RFS), and OS.

In the preoperative design of this phase II trial, we expected that the clinical incidence of toxicities with DGS would increase above that with FP and that the rate of treatment completion would be lower than that in the Japan Clinical Oncology Group (JCOG) study 9907 (89.6%).[26] Accordingly, we assumed a null hypothesis with a 75% completion rate for protocol treatment and expected a completion rate of protocol treatment of 90%. Given a one-sided alpha of 0.1 and statistical power of 80%, a minimum of 28 patients was needed. Assuming a drop-out rate of 10%, the projected sample size was 32 patients.

Relapse-free survival was defined as the time from the date of registration to the first documentation of disease recurrence or any cause of death. Overall survival was measured from the date of registration to the date of the last follow-up or death. Statistical data were calculated with the SPSS 20.0 software package (SPSS, Chicago, IL, USA). The survival curve was estimated using the Kaplan–Meier method.

This trial was registered with the University Hospital Medical Information Network (UMIN ID:000014626).

Results

Patient characteristics. Between March 2010 and June 2015, 32 patients were enrolled in the study. Demographic and clinical characteristics of the study population are summarized in Table 1. All patients had locally advanced esophageal SCC. The median patient age was 67 years (range, 40–82 years), and all patients had an ECOG performance status of 0–1.

Table 1. Characteristics of patients who participated in in a phase II study of docetaxel, nedaplatin, and S1 for advanced esophageal squamous cell carcinoma

Characteristics	No. of patients (n = 32)	%
Age, years		
Median	67	
Range	40–82	
Sex		
Male	29	90.6
Female	3	9.4
ECOG performance status		
0–1	32	100
2	0	0
Site of primary tumor		
Ce	4	12.5
Ut	1	3.1
Mt	15	46.9
Lt	9	28.1
Ae	3	9.4
Clinical T stage		
cT2	8	25.0
cT3	24	75.0
Clinical N stage		
cN0	2	6.3
cN1	8	25.0
cN2	7	21.9
cN3	15	46.9
Clinical stage		
IIB	5	15.6
IIIA	5	15.6
IIIB	3	9.4
IIIC	19	59.4

Ae, abdominal esophagus; Ce, cervical esophagus; ECOG, Eastern Cooperative Oncology Group; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; Ut, upper thoracic esophagus.

Finally, all 32 of the enrolled patients underwent DGS therapy. Except for the first course, which required nutritional management through the nasogastric tube at patient admission due to esophageal stenosis (24 patients [75%]), the therapy could be administered in the outpatient setting.

Toxicity. The overall toxicities experienced by the patients during chemotherapy are listed in Table 2. Leukopenia and neutropenia were the major toxicities. One patient (3.1%) had grade 4 and seven patients (21.9%) had grade 3 neutropenia, and one patient (3.1%) had febrile neutropenia. The eight patients with grade 3/4 neutropenia and the patient with febrile neutropenia received G-CSF. Common non-hematological adverse events included anorexia, mucositis, diarrhea, alopecia, dysgeusia, and hyponatremia. Grade 3 events included mucositis in five patients (15.6%), hyponatremia in five patients (15.6%), and diarrhea in one patient (3.1%). All toxicities were within expectations and were manageable, and no treatment-related deaths occurred.

Surgery and postoperative complications. All patients received surgery as listed in Table 3. Subtotal esophagectomy by right thoracotomy with two- or three-field lymphadenectomy was carried out in 30 patients, and two patients underwent subtotal esophagectomy and lymphadenectomy thoracoscopically. We carried out reconstruction with a stomach roll using the subtotal stomach and a hand-sewn anastomosis in the cervical portion in all patients. Thirty-one patients (96.9%) were considered to have achieved curative resection (R0). One patient (3.1%) had a microscopic residual tumor.

Of the 32 patients who underwent surgery, postoperative complications (grade 2 or more according to National Cancer Institute–Common Terminology Criteria for Adverse Events version 4.0) occurred in three patients (9.4%) in the form of grade 2 recurrent nerve palsy. There were no instances of anastomotic leakage or postoperative death.

Treatment outcomes. All 32 patients completed two courses of chemotherapy, and no patients required a delay of chemotherapy during either of the courses because of adverse events. Six patients required a dose reduction in the second course: four patients with hematological adverse events and two patients with grade 3 mucositis. None of the patients needed more than two extra weeks from the beginning of the first course of chemotherapy until surgery due to adverse events. All of the patients underwent surgery, and one patient was found to require R1 resection pathologically. Thus, the completion rate (completion of the two courses of preoperative chemotherapy and R0 surgery) of the protocol treatment was 96.9%.

Of the 30 patients who had measurable lesions, 8 (26.7%) had complete response and 17 (56.7%) had partial response to therapy, resulting in an overall response rate of 83.3% (95% confidence interval, 65.3–94.4%) (Table 4).

The histological effects in the primary tumors were grade 3 in 5 (15.6%) patients, grade 2 in 9 (28.1%) patients, grade 1b in 2 (6.3%) patients, and grade 1a in 16 (50.0%) patients. In addition, 14 (46.7%) of the 30 patients who were clinically diagnosed as being positive for lymph node metastasis were pathologically node negative, and 3 (10%) patients achieved ypT0N0M0.

With a median follow-up period of 27 months (range, 5–66 months), the rate of estimated 1-year RFS was 73.7%, and that of 1-year OS was 100%. Median RFS was not reached (Fig. 1).

Table 2. Frequency of treatment-related toxicity in a phase II study of docetaxel, nedaplatin, and S1 for advanced esophageal squamous cell carcinoma

	CTCAE version 4.0 common toxicity criteria					
	Grade 1	Grade 2	Grade 3	Grade 4	All grades (%)	Grade 3/4 (%)
Hematologic						
Leucopenia	5	1	2	4	12 (37.5)	6 (18.8)
Neutropenia	2	7	7	1	17 (53.1)	8 (25.0)
Febrile neutropenia	–	–	1	0	1 (3.1)	1 (3.1)
Anemia	0	0	0	0	0 (0.0)	0 (0.0)
Thrombocytopenia	0	2	0	0	2 (6.3)	0 (0.0)
Non-hematologic						
Anorexia	1	5	0	0	6 (18.8)	0 (0.0)
Fatigue	1	0	0	0	1 (3.1)	0 (0.0)
Mucositis	1	4	5	0	10 (31.3)	5 (15.6)
Nausea/vomiting	2	0	0	0	2 (6.3)	0 (0.0)
Diarrhea	2	8	1	0	11 (34.4)	1 (3.1)
Pericardial effusion	–	0	0	0	0 (0.0)	0 (0.0)
Alopecia	19	12	–	–	31 (96.9)	0 (0.0)
Edema	5	0	0	0	5 (15.6)	0 (0.0)
Sensory neuropathy	0	0	0	0	0 (0.0)	0 (0.0)
Dysgeusia	2	1	0	0	3 (9.4)	0 (0.0)
ALT increase	2	1	0	0	3 (9.4)	0 (0.0)
AST increase	3	0	0	0	3 (9.4)	0 (0.0)
Hyponatremia	–	–	5	0	5 (15.6)	5 (15.6)
Creatinine increase	0	0	0	0	0 (0.0)	0 (0.0)

Data represent number of patients. –, no category. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events (National Cancer Institute).

Table 3. Operative details and postoperative outcomes in a phase II study of docetaxel, nedaplatin, and S1 for advanced esophageal squamous cell carcinoma

	No. of patients	%
Surgical approach		
Right thoracotomy	30	93.8
Thoracoscopic surgery	2	6.3
Type of resection		
R0	31	96.9
R1	1	3.1
Postoperative complications		
Recurrent nerve palsy	3	9.4
Pneumonia	0	0
Anastomotic leakages	0	0
Pyothorax	0	0
Pneumothorax	0	0
Chylothorax	0	0
Wound infection	0	0
Heart failure	0	0
Postoperative mortality	0	0

R0, no residual tumor; R1, suspicious of residual tumor or microscopic residual tumor.

Table 4. Overall response in this phase II trial of docetaxel, nedaplatin, and S1 for advanced esophageal squamous cell carcinoma (n = 30)

	n (%)
Complete response	8 (26.7)
Partial response	17 (56.7)
Stable disease	4 (13.3)
Progressive disease	1 (3.3)
Overall response rate	83.3%
Confidence interval	65.3–94.4

Fig. 1. Kaplan–Meier estimates of relapse-free survival (a) and overall survival (b) in a phase II study of docetaxel, nedaplatin, and S1 for advanced esophageal squamous cell carcinoma. The estimated 1-year relapse-free survival and overall survival were 73.7% and 100%, respectively.

Discussion

Esophageal cancer is the ninth most common cancer world-wide and is highly malignant.[27] Additional treatments are currently necessary after surgery or radiotherapy to improve long-term patient outcome. Neoadjuvant chemoradiotherapy is the standard treatment for locally advanced esophageal cancer in Europe and North America.[10] Meanwhile, results of the JCOG 9907 study aided in the approval of neoadjuvant chemotherapy with FP as a standard regimen in Japan.[3] However, there appear to be histological differences in the background of esophageal cancer, and although FP was an effective regimen, the response rate remained unsatisfactory at 38%. Clearly, a new regimen with a high response rate and low toxicity is needed.
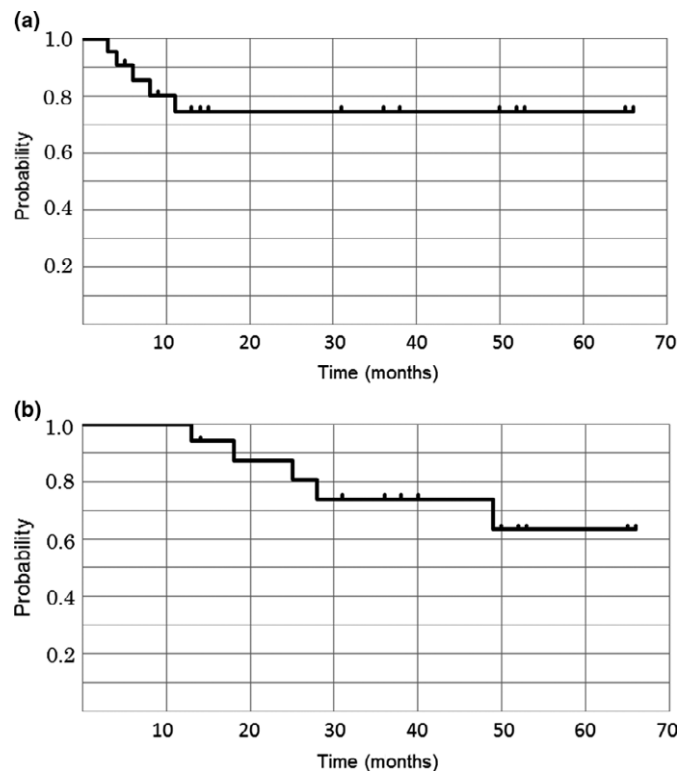
Additionally, a therapy is needed that can be delivered as much as possible in the outpatient setting to maintain high quality of life, one that can be achieved without the necessity of a large amount of fluid infusion or continuous i.v. administration, both of which require hospitalization. Hydration is not required for CDGP administration and S1 is an oral anticancer agent, thus allowing the use of these drugs in the outpatient setting. In this study, except for the first course of DGS, for which 75% of patients required nutritional management through a nasogastric tube at admission, the two courses were given to all patients in the outpatient setting.

Taxanes enhance polymerization of tubulin into stable microtubule formations and inhibit tubulin depolymerization by blockage of the cell cycle in metaphase, anaphase, and interphase.[28] The efficacy of drugs such as CDGP, which is active in all phases of the cell cycle by causing direct DNA damage, may be improved by such inhibition. The taxanes also increase programmed cell death, with TXT being more potent than paclitaxel in the inhibition of angiogenesis.[29]

In the present trial of DGS chemotherapy for esophageal SCC, a combination regimen with DGS was shown to be highly tolerable and effective in patients with clinical stage II/III cancer in a preoperative setting. The activity of the triplet regimen of TXT, CDDP, and 5-FU occurs by synergistic or non-cross-resistance effects when given in combination.[30] Previously published studies have shown that the DCF combination has good efficacy.[31–38] A 34.5–83.3% response rate was observed with DCF combinations used to treat patients with advanced esophageal carcinoma (Table 5). We found that our DGS regimen, similar to the triplet regimen of DCF, also had high a response rate and showed highly promising antitumor activity.

The response rate of histological grade 2/3 tumors was 43.7%, which is satisfactory compared with the 26–51% reported previously.[33,36,37] The results emerging from this phase II study are particularly encouraging. Previous studies indicated that this triplet regimen seems to be not inferior to chemoradiotherapy with respect to the local control rate.[33,39–41] Remarkably, 24 (75.0%) patients in the present study were clinically T3, and the histological effects regarding T3 tumor were grade 3 in 3 (12.5%) patients and grade 2 in 6 (25.0%) patients.

Table 5. Triplet regimen for advanced esophageal cancer (docetaxel, nedaplatin, and S1)

Reference (first author)	Target	Regimen, /m²	Phase	Cases, n	Grade 3/4 leukopenia, %	Grade 3/4 neutropenia, %	Febrile neutropenia, %	Response rate, %	Histopathologic response rate (>grade 2), %	Histopathologic complete response rate (grade 3), %	Dose reduction rate in the second cycle, %	Protocol completion rate, %
Takahashi H[31]	Esophageal cancer (SCC) Stage III, IV	D: 50 (day 1) C: 70 (day 1) F: 700 (days 1–5)/3 wks	I/II	39	53.8	43.6	12.8	66.6	—	—	—	—
Osaka Y[32]	Esophageal cancer (SCC) Stage III, IV	D: 60 (day 1) C: 60 (day 1) F: 800 (days 1–5)/ 3–4 wks × 2 courses	II	30	33.3	—	—	83.3 (primary lesion)	—	—	—	96.7
Yamasaki M[33]	Esophageal cancer (SCC) Stage III, IV	D: 70 (day 1) C: 70 (day 1) F: 700 (days 1–5)/3 wks × 2 courses	I/II	9/40	72.5	90	10	72.5	40	25	—	82.5
Tamura S[34]	Esophageal cancer (SCC) Stage IV	D: 60 (day 1) C: 70 (day 1) F: 600 (days 1–5)/ 4 wks × 2 courses	II	29	52	76	21	34.5 (confirmed cases)	—	—	13.8	—
Ferri LE[35]	Esophageal cancer and gastric cancer (AD) Stage II, III, IV	D: 75 (day 1) C: 75 (day 1) F: 750 (days 1–5)/ 3 wks × 3 courses	II	43	—	20	2.3	—	—	9.8	—	95
Hara H[36]	Esophageal cancer (SCC) Stage IIA, IIB, III	D: 70 (day 1) C: 75 (day 1) F: 750 (days 1–5)/ D: 75 (day 1) C: 75 (day 1) F: 750 (days 1–5)/ 3 wks × 3 courses	II	42	45.2	83.3	2.4	64.3	51	17	64.3	95.2

Table 5 (Continued)

Reference (first author)	Target	Regimen,/m²	Phase	Cases, n	Grade 3/4 leukopenia, %	Grade 3/4 neutropenia, %	Febrile neutropenia, %	Response rate, %	Histopathologic response rate (>grade 2), %	Histopathologic complete response rate (grade 3), %	Dose reduction rate in the second cycle, %	Protocol completion rate, %
Watanabe M[37]	Esophageal cancer (SCC, AD) Stage IIB, III, IVA, IVB (TNM6)	D: 60 (day 1) C:6 (days 1–5)/ F: 350 (days 1–5)/ 3 wks × 2 courses	Prospective intention-to-treat	50	—	78.2	14.5	53.7	26	12	—	—
Hironaka S[38]	Esophageal cancer (SCC, AS, B) Stage IV	D: 30 (days 1, 15) C: 80 (day 1) F: 800 (days 1–5)/ 4 wks	I/II	10/52	9.1	25.5	0	62	—	—	—	—
Current study	Esophageal cancer (SCC) Stage IB, II, III	D: 35 (day 8) CDGP:40 (day 8) S1: 80 (days 1–14)	II	32	18.8	25.0	3.1	83.3	43.7	15.6	18.8	96.9

—, not documented. AD, adenocarcinoma; AS, adenosquamous carcinoma; B, basaloid carcinoma; C, cisplatin; CDGP, nedaplatin; D, docetaxel; F, fluorouracil; SCC, squamous cell carcinoma; wks, weeks.

Therefore, this regimen might lead to the treatment of more cases of locally highly advanced esophageal SCC.

Although outcomes with DCF are favorable, hematological toxicity is an important concern. The high rate of blood toxicity resulting from the administration method used in previous reports caused difficulties in enforcing the regimen in general hospitals. Neutropenia occurs approximately 8–10 days after TXT treatment, but it recovers quickly. Administration of TXT 75–100 mg/m^2 every 3–4 weeks can cause a quite pronounced neutropenia; a rate of febrile neutropenia of up to 44% was reported in patients with recurrent ovarian cancer.[42] Several other reports showed myelosuppression to be the major toxicity of DCF when it was repeated every 3–4 weeks at doses of TXT 50–75 mg/m^2, CDDP 60–75 mg/m^2, and 5-FU 700–800 mg/m^2. Furthermore, frequencies of grade 3/4 leucopenia of 33.3% and neutropenia of 90% were reported in a phase II study[31–38] (Table 5). The incidence of hematological toxicity with our DGS regimen was lower than that in other reports. Although we did not use a prophylactic antimicrobial agent, only one patient developed febrile neutropenia, and no instances of thrombocytopenia ≥grade 3 occurred.

Compared with the DCF regimens used for esophageal cancer in other phase I/II studies[31–38] (Table 5), our regimen included a TXT dose intensity lower than the triweekly administration of TXT used in those studies. However, our DGS regimen reduced myelosuppression while efficacy remained almost unchanged.

The incidence of TXT-specific toxicities, such as neurotoxicity and acute hypersensitivity reactions,[21] in the present phase II trial was relatively low and did not appear to cause major clinical problems. Thus, a reduction in dose was generally not required. This was probably due to the low dose of TXT given each day. Peripheral edema, pleural effusion, or ascites was cumulative in incidence and severity, but no patient experienced severe body-weight gain that required diuretics. Patients receiving more than 50 mg/m^2 CDDP may suffer nausea and vomiting.[43] Both are frequent side-effects and were well controlled in our trial patients by using 40 mg/m^2 CDGP as well as granisetron and dexamethasone. There were no instances of renal dysfunction, and grade 3 events such as mucositis, hyponatremia, and diarrhea were manageable. No treatment-related deaths occurred.

Unless there is almost complete obstruction of the esophagus, S1 can be given by nasogastric tube. In fact, four patients in this study received the first course by nasogastric tube. The first course of DGS subsequently enabled full oral intake in these four patients, and the tube was no longer needed during the second course.

The DGS regimen seemed to be useful as preoperative chemotherapy due to the small need to delay the schedule of anticancer drug administration, and it did not adversely affect the elective surgery schedule. Surgery was carried out according to the schedule in all 32 patients, and no delays were necessary. Moreover, there was no mortality, and no serious postoperative complications occurred. Except for one patient who was found to require R1 resection pathologically, all patients achieved R0 surgery. The completion rate of protocol treatment was 96.9%, which appeared to be satisfactory compared with the JCOG 9907 rate of 89.6%.[26]

Finally, there was concern about whether we could accomplish this DGS regimen in the preoperative setting because the S1 was orally administered. We confirmed that DGS could be safely completed prior to surgery. It might be beneficial to use DGS as neoadjuvant therapy in patients with renal dysfunction, in whom it is preferable to avoid fluid resuscitation as much as possible and who experience difficult hospitalization.

In conclusion, the preoperative DGS regimen was well tolerated and useful for the treatment of resectable esophageal SCC. This regimen shows potential as a candidate component of standard regimens for the treatment of resectable cervical esophageal SCC and thoracic esophageal SCC with cervical lymph node metastasis. Further multicenter, randomized, prospective clinical trials using this triplet combination should be pursued in the treatment of advanced esophageal SCC.

Disclosure Statement

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