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Original Research

Randomized phase II study of docetaxel versus paclitaxel in patients with esophageal squamous cell carcinoma refractory to fluoropyrimidine- and platinum-based chemotherapy: OGSG1201

Sachiko Yamamoto [a], Hisato Kawakami [b,*], Takayuki Kii [c], Hiroki Hara [d], Ryohei Kawabata [e,f], Junji Kawada [g], Atsushi Takeno [h], Jin Matsuyama [i], Shugo Ueda [j], Yoshihiro Okita [k,l], Shunji Endo [m], Yutaka Kimura [f,n], Kazuhiro Yanagihara [o], Tatsuya Okuno [p], Yukinori Kurokawa [q], Toshio Shimokawa [r], Taroh Satoh [s,l]

[a] *Department of Gastrointestinal Oncology, Osaka International Cancer Institute, Osaka, Osaka, 541-8567, Japan*
[b] *Department of Medical Oncology, Kindai University Faculty of Medicine, Osakasayama, Osaka, 589-8511, Japan*
[c] *Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka, 569-0801, Japan*
[d] *Department of Gastroenterology, Saitama Cancer Center, Kitaadachi-gun, Saitama, 362-0806, Japan*
[e] *Department of Surgery, Osaka Rosai Hospital, Sakai, Osaka, 591-8025, Japan*
[f] *Department of Surgery, Sakai City Medical Center, Sakai, Osaka, 593-8304, Japan*
[g] *Department of Surgery, Osaka General Medical Center, Osaka, Osaka, 558-8558, Japan*
[h] *Department of Surgery, Kansai Rosai Hospital, Amagasaki, Hyogo, 660-8511, Japan*
[i] *Department of Surgery, Yao Municipal Hospital, Yao, Osaka, 581-0069, Japan*
[j] *Department of Gastroenterological Surgery and Oncology, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Osaka, 530-8480, Japan*
[k] *Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Hyogo, 650-0047, Japan*
[l] *Department of Clinical Oncology, Kagawa University Faculty of Medicine, Kita-gun, Kagawa, 761-0793, Japan*
[m] *Department of Gastroenterological Surgery, Higashiosaka City Medical Center, Higashiosaka, Osaka, 578-8588, Japan*
[n] *Department of Surgery, Kindai University Faculty of Medicine, Osakasayama, Osaka, 589-8511, Japan*
[o] *Department of Medical Oncology, Kansai Electric Power Hospital, Osaka, Osaka, 553-0003, Japan*
[p] *Division of Gastroenterology, Department of Internal Medicine, Graduate School of Medicine, Kobe University, Kobe, Hyogo, 650-0017, Japan*
[q] *Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, 565-0871, Japan*
[r] *Department of Medical Data Science, Graduate School of Medicine, Wakayama Medical University, Wakayama, Wakayama, 641-8510, Japan*

* *Corresponding author*: Department of Medical Oncology, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-sayama, Osaka, 589-8511, Japan. Fax: +81 72 360-5000.

E-mail address: yamamoto-sa@mc.pref.osaka.jp (S. Yamamoto), kawakami_h@med.kindai.ac.jp (H. Kawakami), in2058@osaka-med.ac.jp (T. Kii), hirhara@cancer-c.pref.saitama.jp (H. Hara), r-kawabata@umin.ac.jp (R. Kawabata), j-kawada@umin.ac.jp (J. Kawada), takeno-atsushi@kansaih.johas.go.jp (A. Takeno), matsuyama-j@higashiosaka-hosp.jp (J. Matsuyama), shu-ueda@kitano-hp.or.jp (S. Ueda), yokita@med.kagawa-u.ac.jp (Y. Okita), endo-s@med.kawasaki-m.ac.jp (S. Endo), you-kimura@med.kindai.ac.jp (Y. Kimura), kazuhiro@kuhp.kyoto-u.ac.jp (K. Yanagihara), t-okuno@pg7.so-net.ne.jp (T. Okuno), ykurokawa@gesurg.med.osaka-u.ac.jp (Y. Kurokawa), shimokaw@wakayama-med.ac.jp (T. Shimokawa), taroh@cfs.med.osaka-u.ac.jp (T. Satoh).

[1] For Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG).

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[s] Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Osaka, 565-0871, Japan

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KEYWORDS
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Abstract ***Background:*** There is no standard chemotherapy for esophageal squamous cell carcinoma (ESCC) refractory to first-line fluoropyrimidine- and platinum-based chemotherapy. We therefore performed a randomized, selection-design phase II trial to compare docetaxel (DTX) and paclitaxel (PTX) in this setting.
Patients and methods: Eligible patients were randomly assigned to receive either DTX (70 mg/m^2 on day 1 of each 21-day cycle) or PTX (100 mg/m^2 on days 1, 8, 15, 22, 29 and 36 of each 49-day cycle). The primary end-point was overall survival (OS), and secondary end-points included progression-free survival (PFS), time to treatment failure (TTF), response rate (RR) and safety.
Results: Seventy-eight eligible patients ($N = 39$ in each group) were included for efficacy analysis. OS was significantly longer in the PTX group than in the DTX group (median, 8.8 versus 7.3 months; hazard ratio [HR], 0.62; $P = 0.047$). A significant benefit of PTX over DTX was also apparent in PFS (median, 4.4 versus 2.1 months; HR, 0.49; $P = 0.002$) and TTF (median, 3.8 versus 2.1 months; HR, 0.45; $P < 0.001$). RR (25.6% versus 7.7%, $P = 0.065$) were higher in the PTX group than in the DTX group. Compared to the PTX group, neutropenia (28% versus 80%) and leukopenia (28% versus 76%) of grade $\geq$3 as well as febrile neutropenia (0% vs. 46%, $P < 0.0001$) occurred more frequently in the DTX group.
Conclusion: PTX showed a significantly better efficacy as well as a more manageable toxicity compared with DTX.
Clinical trial registration: UMIN000007940.

1. Introduction

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide [1]. While the incidence of esophageal adenocarcinoma is rapidly increasing in Europe [2] and North America [3,4], esophageal squamous cell carcinoma (ESCC) remains the most common esophageal tumor type globally [4,5] including in Japan [6]. The overall survival of individuals with esophageal cancer, regardless of histological type, remains poor. Fluoropyrimidine- and platinum-based chemotherapy is considered a first-line treatment option for patients with unresectable advanced or recurrent metastatic ESCC [5,6], given a paucity of specific evidence based on phase III studies. Phase II clinical studies for the combination of cisplatin and 5-fluorouracil (5-FU) yielded a response rate of ~30% and a median survival time (MST) of 6.6–9.5 months [7–10]. As an alternative to cisplatin, nedaplatin and oxaliplatin are options for patients who are not able to tolerate cisplatin as a result of impaired renal or cardiac function [11,12].

Although there is currently no accepted standard chemotherapy after patients with ESCC become refractory to fluoropyrimidine- and platinum-based chemotherapy [13], taxanes have been examined in this setting in Japan. A single-arm phase II study found that docetaxel (DTX) alone at 70 mg/m^2 once every 3 weeks showed a response rate of 16% and MST of 8.1 months [14]. Adverse events (AEs) were within a permissible range in patients with a good performance status, whereas serious AEs of grade $\geq$3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 were encountered at an incidence of ~10%–20% among patients. Treatment with another taxane, paclitaxel (PTX), at 100 mg/m^2 weekly for 6 weeks, repeated at 7-week intervals, showed promising results, with a response rate of 44.2% and MST of 10.4 months [15]. Retrospective studies comparing DTX and PTX in patients refractory to fluoropyrimidine- and platinum-based chemotherapy suggested similar clinical efficacies, with an MST of 5.5–6.1 months versus 6.1–7.2 months, respectively, but different toxicity profiles, with a higher incidence of hematologic toxicity and febrile neutropenia for DTX than for PTX [16,17]. However, no comparative prospective studies of DTX versus PTX for ESCC in this setting have been reported.

We have now conducted a randomized phase II trial to compare DTX and PTX in patients with unresectable advanced or recurrent ESCC who had become refractory to previous fluoropyrimidine- and platinum-based chemotherapy.

2. Methods

2.1. Patients

Eligible patients were aged 20–80 years and had unresectable advanced or recurrent esophageal cancer that was pathologically confirmed as squamous or adenosquamous cell carcinoma. Inclusion criteria comprised an Eastern Cooperative Oncology Group performance status of 0 or 1; refractoriness to fluoropyrimidine- and platinum-based chemotherapy; an interval of <24 weeks either from the date of surgery in patients who received neoadjuvant chemotherapy or from the last dose of adjuvant chemotherapy associated with radical resection; adequate hematologic, renal and hepatic function; and provision of written informed consent. Exclusion criteria included interstitial lung disease or pneumonitis, a history of taxane (DTX or PTX) treatment, active multiple cancers, and a history of nerve disorders of grade 2 to 4 according to NCI-CTCAE version 4.0.

2.2. Trial design and treatment

In this randomized, open-label phase II study (OGSG1201), eligible patients were allocated in a 1:1 ratio to DTX (70 mg/m^2 on day 1 of each 21-day cycle) or PTX (100 mg/m^2 on days 1, 8, 15, 22, 29 and 36 of each 49-day cycle). Random assignment was stratified by investigator institute and primary tumor (present versus absent). To equate the assessment of adverse events with PTX, patients assigned to DTX were assessed weekly for adverse events until day 49. Treatment with DTX or PTX was continued until documented disease progression, the development of unacceptable toxicity, dose reduction below the minimum dose, or treatment interruption for >21 days as a result of AEs or a decision of the physician or patient to withdraw. All patients gave written informed consent. The study was approved by the institutional review board at each participating site and was independently monitored by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) data center. The trial was registered in the University Hospital Medical Network Clinical Trials Registry in Japan (UMIN000007940; http://www.umin.ac.jp/ctr/).

2.3. Assessments and outcomes

The primary end-point of the study was overall survival (OS). Secondary end-points were progression-free survival (PFS), time to treatment failure (TTF), response rate (RR) and AEs.

Tumor response was assessed by the investigator from computed tomography (CT) or other images according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Imaging was performed at baseline and every 8 weeks thereafter until unacceptable toxicity or disease progression. Survival was assessed every 6 months during follow-up. Complete and partial responses were confirmed by two scans performed with an interval of ≥4 weeks. AEs were assessed throughout the study and graded according to NCI-CTCAE version 4.0.

2.4. Statistical analysis

The study was designed as a randomized selection phase II trial to compare PTX with DTX as a basis for a future phase III trial. The median OS expected on the basis of the results of previous studies [14,16,17] was 6 months. The number of patients required was calculated on the basis of a selection design so that the test arm would select a regimen with a median OS that was 2 months longer than the expected value with 80% probability. A total of 38 patients per group was thus required, and the number of patients to be enrolled was set at 40 per group to allow for some deviation.

The primary analysis was based on the full analysis set (FAS), which consists of all randomized patients except those who were found to be ineligible after enrollment. We used the Kaplan–Meier method to estimate survival curves and Greenwood's formula to calculate 95% confidence intervals (CIs) for median survival rates. A log-rank test was applied to comparison of survival curves. A Cox proportional hazards model was applied to calculate HRs and 95% CIs. The Fisher's exact test was used to compare the RR, disease control rate (DCR; proportion of patients with confirmed CR, PR or stable disease), the AEs of PTX to DTX, and for the association between history of radiotherapy and interstitial pneumonia. All statistical analysis was performed with the use of R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria) or SAS version 9.4 (SAS Institute, Cary, NC). A P value of <0.05 was considered statistically significant.

3. Results

3.1. Patients

Between 1st May 2011 and 30th April 2019, a total of 80 patients from 17 institutions of the OGSG was enrolled in the study and underwent randomization to receive either DTX (N = 41) or PTX (N = 39). All patients received at least one dose of the assigned treatment.

Given that two patients in the DTX group were found to be ineligible either because of the discovery of multiple cancers or because of a history of receiving DTX as neoadjuvant chemotherapy (DTX + cisplatin + 5-FU regimen), 78 eligible patients (DTX group, $N = 39$; PTX group, $N = 39$) were included in the full analysis set for assessment of OS, PFS, TTF and RR (Fig. 1). Patient characteristics were found to be balanced between the two arms of the study (Table 1). The number of patients with measurable lesion was 33 in the DTX group and 29 in the PTX group. Cisplatin was the most common immediate prior platinum (DTX group, $N = 35$; PTX group, $N = 34$), whereas nedaplatin was used in 11 cases (DTX group, $N = 6$; PTX group, $N = 5$) (Table 1). Most cases (97.5%, 78/80) received prior fluoropyrimidine- and platinum-based chemotherapy in a palliative setting, whereas two cases (DTX group, $N = 1$; PTX group, $N = 1$) received it in a perioperative setting. Of the 78 patients received fluoropyrimidine- and platinum-based chemotherapy in the palliative setting, 28 had recurrence after esophagectomy (DTX group, $N = 13$; PTX group, $N = 15$). Including cases in which the primary lesion disappeared with chemoradiotherapy, the total number of patients without primary tumor was 16 for the DTX group and 19 for the PTX group, accordingly (Table 1 and Supplementary Fig.).

3.2. Treatment delivery

Analysis was conducted 1 year after closure of recruitment, at which time (April 2020) all patients had discontinued treatment. The main reason for treatment discontinuation was progressive disease (75%, $N = 60$; $N = 33$ for DTX versus $N = 27$ for PTX). Relative dose intensity for DTX was similar to that for PTX (mean ± SEM of 85.6 ± 12.4% versus 83.2 ± 14.3%, respectively).

3.3. Safety

The main hematologic and nonhematologic AEs in the two treatment groups are listed in Table 2. One sudden death without known cause occurred in the DTX group and was considered to be treatment related by the Data and Safety Monitoring Committee. The most common any-grade hematologic AE was anaemia, which occurred at a similar frequency in both treatment groups. In contrast, neutropenia occurred more frequently in the DTX group than in the PTX group, with the incidence of such events of grade 3 or 4 that required drug interruption or dose reduction also being higher in the DTX group.

Based on the efficacy and safety monitoring conducted at the time of enrollment of 48 patients, the protocol was amended (in March 2015) to recommend the prophylactic use of G-CSF in the DTX group because of the high incidence of febrile neutropenia. Nevertheless, febrile neutropenia was significantly more frequent in the DTX group than in the PTX group (46% versus 0%, $P < 0.0001$). Anorexia, fatigue and hypoalbuminemia were common any-grade AEs with a higher frequency in the DTX group than in the PTX group, with the incidence of these events of grade ≥3

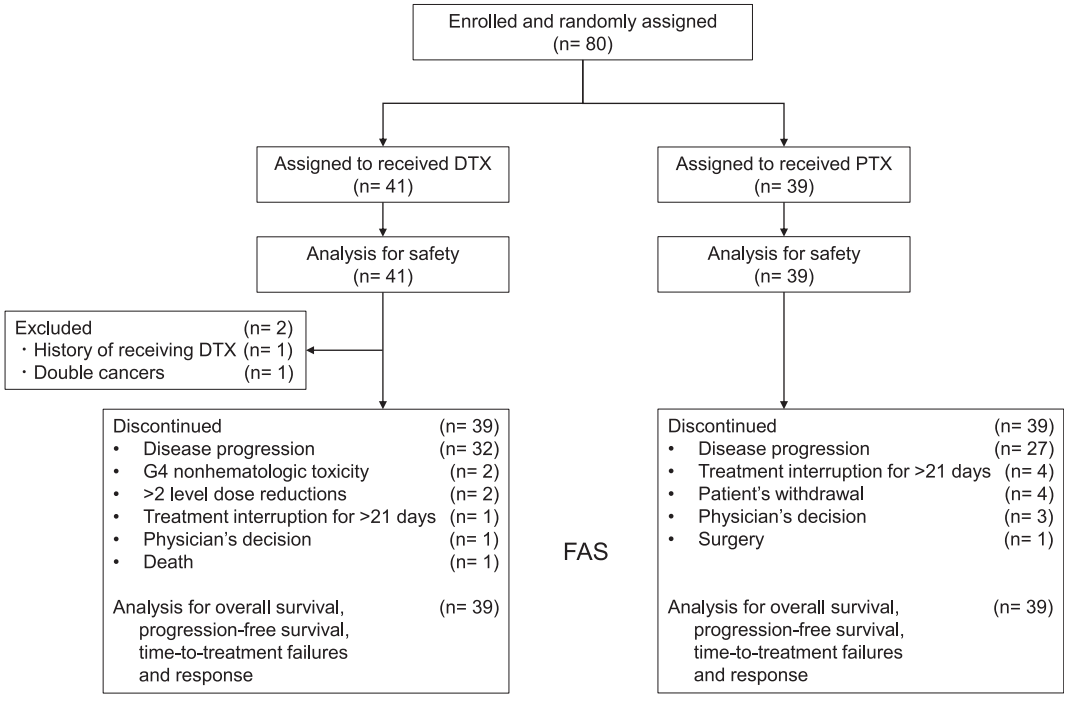

Fig. 1. CONSORT diagram. Abbreviations not defined in text: DTX, docetaxel; PTX, paclitaxel; G4, grade 4; FAS, full analysis set.

Table 1
Patient characteristics.

Characteristic	DTX (N = 41)	PTX (N = 39)
Age (years)		
Median (range)	69 (47–83)	67 (48–78)
Sex		
Male	38	35
Female	3	4
ECOG performance status		
0	23	21
1	18	18
Location of primary tumor		
Ce	2	2
Ut	11	10
Mt	16	13
Lt	10	12
Ae	2	2
Histology type		
Well-differentiated SCC	5	6
Moderately differentiated SCC	17	19
Poorly differentiated SCC	9	4
SCC	9	7
Adenosquamous cell carcinoma	0	3
High grade	1	0
Measurable lesions		
Present	33	29
Absent	8	10
Number of organs with metastases		
1	21	21
2	15	14
3	3	3
4	2	1
Sites of metastases		
Lymph node	26	31
Lung	15	8
Liver	8	10
Bone	5	5
Pleura	2	2
Peritoneum	1	3
Other	4	1
Prior chemotherapy		
FP	35	34
5-FU+nedaplatin	6	5
Primary tumor		
Present	25	20
Absent	16	19
History of radiotherapy		
Yes	15	16
No	26	23
History of esophagectomy		
Yes	14	16
Neoadjuvant or adjuvant chemotherapy	10	9
FP	4	6
DCF	1	0
FAP	3	0
FP + radiotherapy	2	3
No	27	23

DTX, docetaxel; ECOG, Eastern Cooperative Oncology Group; PTX, paclitaxel; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; SCC, squamous cell carcinoma; FP, 5-fluorouracil (5-FU) + cisplatin; DCF, docetaxel + cisplatin + 5-FU; FAP, 5-FU + adriamycin + cisplatin.

(anorexia, fatigue, hypoalbuminemia) also being higher in the DTX arm. In contrast, neuropathy developed more frequently in the PTX group than in the DTX group. Other serious nonhematologic AEs included interstitial pneumonia (N = 3 and 1 in the DTX and PTX groups, respectively), with one case in each treatment group developing to grade 3 or 4. No causal relation was apparent between interstitial pneumonia and history of radiation therapy (P = 0.293).

3.4. Efficacy

For survival analysis, the median follow-up time was 8.0 months (range, 1.3–54.4 months). OS was significantly longer in the PTX group than in the DTX group (median, 8.8 months, with a 95% CI of 7.9–17.9 months, versus 7.3 months, with a 95% CI of 5.3–11.0 months; hazard ratio [HR] of 0.62, with a 95% CI of 0.38–0.99; P = 0.047) (Fig. 2). A significant benefit for PTX over DTX was also apparent with regard to PFS (median, 4.4 months [95% CI, 3.8–5.6 months] versus 2.1 months [95% CI, 2.1–2.9 months]; HR of 0.49 [95% CI, 0.30–0.78]; P = 0.002) (Fig. 3A) and to TTF (median, 3.8 months [95% CI, 3.5–4.4 months] versus 2.1 months [95% CI, 2.0–2.4 months]; HR of 0.45 [95% CI, 0.28–0.73]; P < 0.001) (Fig. 3B). The RR for the FAS was 25.6% (95% CI, 13.0–42.1%) in the PTX group and 7.7% (95% CI, 1.6–20.9%) in the DTX group, although this difference did not achieve statistical significance (P = 0.065) (Table 3). The DCR for the FAS was significantly higher in the PTX group than in the DTX group (74.4% versus 35.9%, P = 0.0013).

3.5. Poststudy treatment

Among the 78 patients analyzed, 44 individuals received subsequent therapy (Supplementary Table). Of note, 24 patients, comprising 14 in the DTX group and 10 in the PTX group, received subsequent crossover treatment (that is, DTX followed by PTX, or PTX followed by DTX). Patients who received such crossover therapy showed a significantly longer OS compared with those who received other poststudy treatment (HR of 0.40 [95% CI, 0.23–0.71], P = 0.002), with the survival benefit of such treatment being apparent in the DTX group (HR of 0.30 [95% CI, 0.14–0.65], P = 0.002) but not in the PTX group (HR of 0.58 [95% CI, 0.26–1.28], P = 0.171).

4. Discussion

As far as we are aware, this study is the first to prospectively compare the safety and efficacy of DTX and PTX in the second-line setting for patients with ESCC refractory to chemotherapy with 5-FU and a platinum agent. With regard to DTX, the previous study reported a RR of 16% and MST of 8.1 months [14], with a

Table 2
Numbers (%) of patients with main adverse events.

Event	DTX (N = 41)					PTX (N = 39)			
	All grade (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	Grade 3–5 (%)	All grade (%)	Grade 3 (%)	Grade 4 (%)	Grade 3 or 4 (%)
Neutropenia	34 (83)	8 (20)	25 (61)	0	33 (80)	25 (64)	8 (21)	3 (8)	11 (28)
Leukopenia	34 (83)	19 (46)	12 (29)	0	31 (76)	30 (77)	10 (26)	1 (3)	11 (28)
Anaemia	36 (88)	11 (27)	0	0	11 (27)	34 (87)	4 (10)	1 (3)	5 (13)
Thrombocytopenia	13 (32)	0	0	0	0	6 (15)	0	0	0
Febrile neutropenia	19 (46)	18 (44)	1 (2)	0	19 (46)	0	0	0	0
Anorexia	31 (76)	6 (15)	0	0	6 (15)	20 (51)	2 (5)	0	2 (5)
Fatigue	30 (73)	5 (12)	0	0	5 (12)	22 (56)	1 (3)	0	1 (3)
Infection	9 (22)	2 (5)	2 (5)	0	4 (10)	9 (23)	2 (5)	0	2 (5)
Neuropathy	5 (12)	0	0	0	0	28 (72)	3 (8)	0	3 (8)
Hyponatremia	8 (20)	3 (7)	0	0	3 (7)	2 (5)	0	0	0
Hypoalbuminemia	31 (76)	2 (5)	0	0	2 (5)	15 (38)	0	0	0
Interstitial pneumonia	3 (7)	0	1 (2)	0	1 (2)	1 (3)	1 (3)	0	1 (3)
Diarrhea	12 (29)	1 (2)	0	0	1 (2)	8 (21)	1 (3)	0	1 (3)
Edema	4 (10)	0	0	0	0	4 (10)	1 (3)	0	1 (3)
Myalgia	2 (5)	0	0	0	0	1 (3)	1 (3)	0	1 (3)
AST increased	12 (29)	1 (2)	0	0	1 (2)	8 (21)	0	0	0
Hypokalemia	3 (7)	1 (2)	0	0	1 (2)	1 (3)	0	0	0
Hyperkalemia	5 (12)	1 (2)	0	0	1 (2)	4 (10)	0	0	0
Hypercalcemia	1 (2)	1 (2)	0	0	1 (2)	2 (5)	0	0	0
Alopecia	22 (54)				0	25 (64)			0
Sudden death	1 (2)	0	0	1 (2)	1 (2)	0	0	0	0
GGT increased	0	0	0	0	0	2 (5)	1 (3)	0	1 (3)
Hyperglycemia	0	0	0	0	0	3 (8)	1 (3)	0	1 (3)
Nausea	10 (24)	0			0	11 (28)	0		0
Anaphylaxis	0 (0)	0	0	0	0	1 (3)	1 (3)	0	1 (3)

DTX, docetaxel; PTX, paclitaxel; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase.

relatively high incidence of hematologic toxicity, including 24% and 73% for leukopenia and neutropenia of grade 4, respectively, as well as 18% for febrile neutropenia. The previous study of PTX reported a RR of 44.2% and MST of 10.4 months [15], with generally mild hematologic toxicity, including an incidence of 45% and 53% for leukopenia and neutropenia of grade 3 or 4, respectively, and a relatively low frequency of febrile neutropenia (4%). This suggestion of a better efficacy for PTX versus DTX [14,15] was confirmed in the present study, which detected significant improvements in OS, PFS, and TTF and a trend toward an improved RR for PTX. The survival benefit of PTX apparent for PFS seemed to be attenuated for OS, likely as a result in part by the salvage PTX treatment in the DTX group.

Our study found that toxicity, especially hematologic toxicity, tended to be greater for DTX than for PTX, consistent with the results of previous retrospective studies [16,17]. Of note, the frequency of neutropenia of grade 4 was markedly higher for the DTX arm than for the PTX arm (61% vs. 8%), resulting in a significantly higher incidence of febrile neutropenia for DTX (46% versus 0%, $P < 0.0001$), although the prophylactic use of G-CSF was recommended for DTX after the amendment of the study protocol. The higher febrile neutropenia incidence in the current study compared with that of 12–30% in the other first-line trials including other cancer types with DCF regimens [18–22] may reflect the poor condition of ESCC patients after failure of the first-line treatment. The efficacy and toxicity of

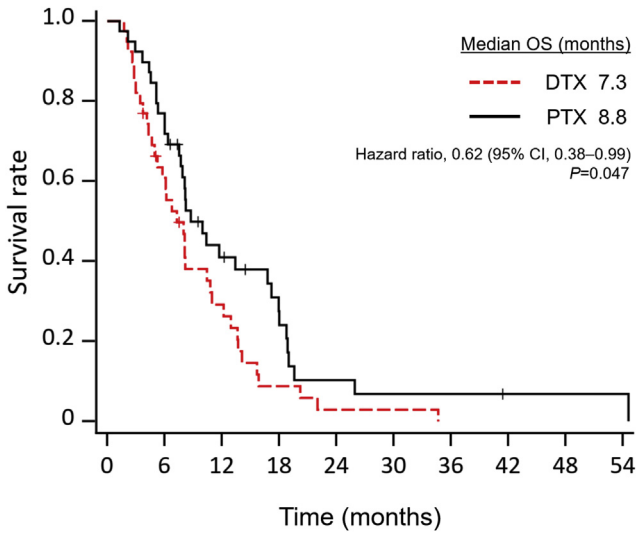

Fig. 2. Kaplan–Meier curves for overall survival. Dashed red line and solid black line indicate docetaxel (DTX) and paclitaxel (PTX) groups, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

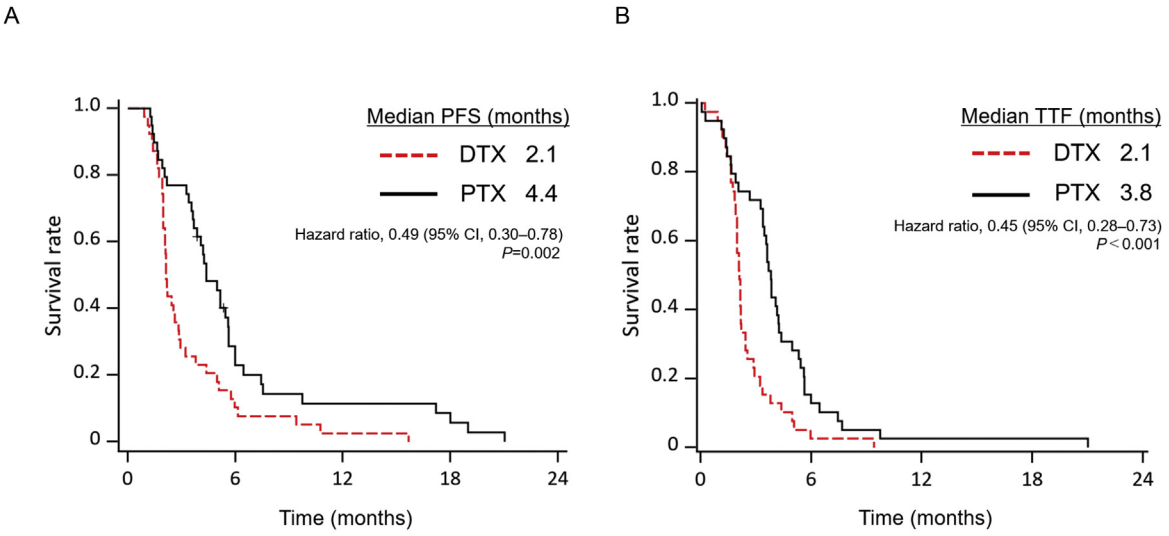

Fig. 3. Kaplan–Meier curves for progression-free survival (A) and time to treatment failure (B). Dashed red line and solid black line indicate docetaxel (DTX) and paclitaxel (PTX) groups, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

PTX thus differed substantially from those of DTX even though both agents are taxanes. These differences might be due in part to differences in dosing, given that previous studies have suggested that split dosing of DTX can reduce hematologic toxicity without compromising therapeutic efficacy [23] in the first-line setting [24–27]. Further studies are thus warranted to optimize the use of DTX in the setting of the present study.

Monotherapy with the immune checkpoint inhibitors (ICIs) nivolumab or pembrolizumab has been proposed as a standard of care for second-line treatment of ESCC after the failure of fluoropyrimidine- and platinum-based chemotherapy on the basis of the ATTRACTION-3 [28] and KEYNOTE-181 [29] phase III studies. In these studies, ICI monotherapy thus showed a significant survival benefit over chemotherapy of the physician's choice [28,29]. In the ATTRACTION-3 study, the chemotherapy arm consisted of treatment with PTX (the same dosing as in the present study) and DTX (75 mg/m^2 on day 1 of each 21-day cycle), showing an MST of 8.4 months, median PFS of 3.9 months, and RR of 22% [28]. In the KEYNOTE-181 study, the chemotherapy arm consisted of treatment with PTX (80–100 mg/m^2 on days 1, 8 and 15 of each 28-day cycle), DTX (75 mg/m^2 on day 1 of each 21-day cycle) and irinotecan (180 mg/m^2 on day 1 of each 14-day cycle), showing an MST of 7.1 months, median PFS of 3.4 months, and RR of 6.7% [29]. Compared with the data for these two previous studies, the PTX group in the present study demonstrated reasonable survival, supporting the use of PTX in the second-line setting for patients with ESCC.

Table 3
Objective response rate among patients with measurable lesions.

Variable	DTX (N = 39)	PTX (N = 39)
Complete response	0	0
Partial response	3 (7.7%)	10 (25.6%)
Stable disease	11 (28.2%)	19 (48.7%)
Progressive disease	24 (61.5%)	8 (20.5%)
Not evaluable	1 (2.6%)	2 (5.1%)
Response rate (%)	7.7 (95% CI, 1.6–20.9)	25.6 (95% CI, 13.0–42.1)
	P = 0.065	
Disease control rate (%)	35.9 (95% CI, 22.7–51.6)	74.4 (95% CI, 58.8–85.6)
	P = 0.0013	

DTX, docetaxel; PTX, paclitaxel; CI, confidence interval. P values for comparisons between the two groups were determined with Fisher's exact test.

This study has several limitations. First, the relatively sample size of this study. The number of patients was set based on the 'selection design' that is intended to prioritize two or more study treatments and is not a validation study design. It is thus important to be reminded that a future phase III trial is necessary to reach a confirmatory conclusion. Second, as with other physician-led studies, this was an open-label study and the antitumor effects were not assessed by the blinded independent central review, but by the investigators. Third, it has taken 8 years to complete this study, although 3 years was firstly set as the enrollment period. Possible reasons for this included that few cases could meet the eligibility criteria for the study as ESCC patients after the first-line treatment were generally in poor condition and that other trials evaluating ICIs in the previously treated ESCC were running at the same period.

In conclusion, our results provide evidence of a better efficacy and safety for PTX than DTX as the second-line

chemotherapy for patients with ESCC. Given that a recent phase III study showed a survival benefit for the addition of pembrolizumab compared with that of placebo to the combination of 5-FU and cisplatin for esophageal cancer patients [30], and another recent study has demonstrated the efficacy of the combination of the ICIs ipilimumab and nivolumab or that of 5-FU plus cisplatin plus nivolumab compared with 5-FU plus cisplatin for ESCC [31], treatment with ICIs with or without chemotherapy now has become the standard of care for ESCC patients in the first-line setting. This scenario highlights the need for a standard second-line treatment not reliant on ICIs. Given the clear difference in efficacy and safety for PTX over DTX revealed in the present study, PTX may become a control arm in future phase III studies after first-line treatment with an ICI-containing regimen.

CRediT author statement

Sachiko Yamamoto: Conceptualization, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing- Reviewing and Editing. **Hisato Kawakami:** Resources, Visualization, Writing – original draft, Writing- Reviewing and Editing. **Takayuki Kii:** Conceptualization, Methodology, Project administration, Resources, Writing- Reviewing and Editing. **Hiroki Hara:** Resources, Writing-Reviewing and Editing. **Ryohei Kawabata:** Resources, Writing- Reviewing and Editing. **Junji Kawada:** Resources, Writing- Reviewing and Editing. **Atsushi Takeno:** Resources, Writing- Reviewing and Editing. **Jin Matsuyama:** Resources, Writing- Reviewing and Editing. **Shugo Ueda:** Resources, Writing- Reviewing and Editing. **Yoshihiro Okita:** Resources, Writing- Reviewing and Editing. **Shunji Endo:** Resources, Writing-Reviewing and Editing. **Yutaka Kimura:** Resources, Writing- Reviewing and Editing. **Kazuhiro Yanagihara:** Resources, Writing- Reviewing and Editing. **Tatsuya Okuno:** Resources, Writing- Reviewing and Editing. **Yukinori Kurokawa:** Data curation, Formal analysis, Investigation, Project administration, Validation, Visualization. **Toshio Shimokawa:** Data curation, Formal analysis, Investigation, Software, Validation, Visualization. **Taroh Satoh:** Funding acquisition, Supervision.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **HK** has received consulting fees and research funding from Bristol-Myers Squibb Co. Ltd. as well as honoraria and lecture fees from Bristol-Myers Squibb Co. Ltd. and Takeda Pharmaceutical Co. Ltd. **HH** has received honoraria from Bristol-Myers Squibb Co. Ltd., Yakult Honsha Co. Ltd., Sanofi K. K., and Takeda Pharmaceutical Co. Ltd., as well as research funding from Bristol-Myers Squibb Co. Ltd., Yakult Honsha Co. Ltd., Sanofi K. K., Takeda Pharmaceutical Co. Ltd., and Pfizer Japan Inc. **Y Kurokawa** has received lecture fees from Bristol-Myers Squibb Co. Ltd., Yakult Honsha Co. Ltd., Takeda Pharmaceutical Co. Ltd., Nippon Kayaku Co. Ltd., and Pfizer Japan Inc. **T Satoh** has received grants and other funding from Yakult Honsha Co. Ltd. and Bristol-Myers Squibb Co. Ltd. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

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