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Evaluation of second-line treatment options in metastatic esophageal squamous cell carcinoma

Yonca Yılmaz Ürün[1], Muslih Ürün[2]

[1]Department of Gastroenterology and Hepatology, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye
[2]Department of Medical Oncology, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye

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Corresponding Author: Yonca Yılmaz Ürün, dryoncayilmazurun@gmail.com

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ABSTRACT

Aims: Esophageal cancer is the seventh most common cause of death worldwide and the survival rate of patients with metastatic esophageal cancer is very low. Although current guidelines recommend immunotherapy as a second-line treatment for esophageal squamous cell carcinoma (SCC), a significant proportion of patients have difficulty accessing this treatment. Therefore, conventional chemotherapy is used as second-line treatment. In this study, we aimed to compare the efficacy and tolerability of irinotecan- and taxane-containing chemotherapy regimens as second-line treatments for patients with disease progression after first-line cytotoxic chemotherapy.

Methods: This study included 43 patients with metastatic esophageal SCC at the time of diagnosis or relapse during follow-up. The patients were divided into two groups: irinotecan-based chemotherapy regimens (n=21) and taxane-based chemotherapy regimens (n=22). Demographic characteristics, treatment regimens, treatment responses, grade 3-4 toxicities, overall survival (OS), and progression-free survival (PFS) were documented and analyzed using appropriate statistical methods.

Results: Of the 43 patients who received second-line treatment, 25 (58.1%) were male and 18 (41.9%) were female. The mean age was 55.86±11.6 years. At the time of diagnosis, 72.1% of the patients had metastatic disease. The median OS was 5 months (95% CI, 2.5 to 7.4) for the irinotecan-based regimen and 10 months (95% CI, 2.6 to 17.3) for the taxane-based regimen (p=0.122). The median PFS was 4 months (95% CI, 2.9 to 5.0) in the irinotecan-based regimen group and 7 months (95% CI, 4.8 to 9.1) in the taxane-based regimen group (p=0.80). There were no significant differences in OS and PFS between the two groups. Grade 3-4 neutropenia (p=0.046) and grade 3-4 neuropathy (p=0.034) were higher in the group receiving taxane-based regimens, while grade 3-4 mucositis (p=0.027) was higher in the group receiving irinotecan-based regimens. There were no statistically significant differences in other side effects (p>0.05).

Conclusion: We found no statistically significant difference in the median PFS and median OS between the two chemotherapy groups used as second-line treatment for metastatic esophageal SCC. Grade 3-4 neutropenia and grade 3-4 neuropathy were higher in the group receiving taxane-based regimens, while grade 3-4 mucositis was higher in the group receiving irinotecan-based regimens. Although our study has limitations, such as its retrospective and single-center nature, it is one of the few studies performed in this patient group in recent years and is important because it reflects our clinical practice.

Keywords: Esophageal cancer, squamous cell carcinoma, second-line treatment

INTRODUCTION

Esophageal cancer is the seventh most common cause of death worldwide, accounting for >400.000 deaths annually.[1] There are two predominant subtypes of cancer, squamous cell carcinoma (SCC) and adenocarcinoma. These subtypes differ in several characteristics, including tumor location and predisposing factors. Smoking and alcohol use are the main risk factors for SCC, while Barrett's esophagus, obesity and smoking are risk factors for adenocarcinoma.[2] Although the adenocarcinoma subtype is more common in western countries, the predominant subtype is SCC.[3] More than one-third of the patients with esophageal cancer are diagnosed at the metastatic stage.[4] The prognosis of metastatic disease is extremely poor, with a 5-year survival rate of approximately 5%.[5]

Both Eastern and Western guidelines recommend endoscopic treatment or upfront surgery for early stage tumors, whereas surgery after neoadjuvant therapy is recommended for locally advanced diseases. Palliative chemotherapy, immunotherapy, and targeted therapies are recommended for the treatment of metastatic diseases. For second-line treatment, immunotherapy is recommended for patients with access to immunotherapy, while palliative chemotherapy is recommended for other patients.[6-8]

Phase-2 trials of paclitaxel[9], docetaxel[10] and irinotecan[11], chemotherapies in second-line treatment are available and have shown modest survival. Among immunotherapy agents, which are now an important part of oncologic treatment, there are four phase-3 studies with positive results. In the KEYNOTE-181 study, pembrolizumab was compared with conventional chemotherapy, and pembrolizumab improved overall survival (OS).[12] In the ATTRACTION-3 study, nivolumab was superior to taxanes (paclitaxel and docetaxel) in terms of OS.[13] The ESCORT study also showed a survival advantage of camrelizumab over chemotherapy.[14] Finally, the RATIONALE-302 study demonstrated the superiority of tislelizumab over taxanes and irinotecan.[15]

Although current guidelines recommend immunotherapy as second-line treatment for esophageal SCC in patients with access, a significant proportion of patients worldwide have problems accessing this treatment. Currently, there are no widely accepted chemotherapy regimens for patients who cannot receive immunotherapies. The aim of our study was to compare the efficacy and tolerability of irinotecan- and taxane-containing chemotherapy regimens, which are widely used worldwide and an important part of our clinical practice, as second-line treatments in patients who progress after first-line cytotoxic chemotherapy.

METHODS

Ethics

Ethical approval was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2023, Decision No: 2023/09-01). The requirement for informed consent was waived owing to the retrospective nature of the study. All procedures were performed in accordance with. Ethical rules and principles of the Declaration of Helsinki.

Study Population

Esophageal SCCs treated and followed up at Van Yüzüncü Yıl University Medical Faculty Hospital between January 2011 and December 2023 were screened. The inclusion criteria were as follows: (1) age >18 years; (2) cytologically or histologically proven metastatic esophageal SCC; (3) treatment regimens including irinotecan, paclitaxel, or docetaxel; (4) previous treatment for recurrent metastatic disease and progression; and (5) at least two cycles of chemotherapy. Exclusion criteria were: (1) younger than 18 years of age; (2) no pathologic or cytologic diagnosis; (3) non-SCC subtypes; (4) no prior treatment for recurrent metastatic disease; (5) patients receiving treatment other than chemotherapy (such as targeted therapies and immunotherapies); (6) patients whose chemotherapy regimen did not include irinotecan or taxane group chemotherapy; and patients with missing data. Patients enrolled in the study received irinotecan-based regimens as second-line chemotherapy if they received taxane-based chemotherapy as first-line chemotherapy, and taxane-based chemotherapy as second-line chemotherapy if they did not receive taxane-based chemotherapy as first-line chemotherapy. Patients were screened prior to treatment by history and physical examination for the presence of potential side effects that may occur with second-line chemotherapy, and no findings related to potential side effects were noted in any of the patients.

Evaluation

The medical records of the patients were collected, including demographic characteristics, treatment regimens and responses to treatment, grade 3-4 toxicities, date of progression, date of the last follow-up, and date of death. Performance scores were assessed according to the Eastern Cooperative Oncology Group (ECOG) criteria. Progression-free survival (PFS) was calculated as the time from second-line treatment to the date of progression or death. OS was calculated as the time from the start of second-line treatment until death or last follow-up. Patients were divided into two groups: those receiving irinotecan-based chemotherapy regimens (irinotecan-folinic acid-fluorouracil (FOLFIRI) and irinotecan) and those receiving taxane-based chemotherapy regimens (paclitaxel and docetaxel). Radiological evaluations were performed every eight weeks if there was no clinical progression. The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Toxicity was assessed by physical examination, medical history and biochemical tests on day 1 of each cycle. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0). Only grade 3-4 toxicities were observed.

Statistical Analysis

The data analyses were conducted using IBM SPSS Statistics for Windows Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as n and % for categorical variables, and as median (min–max) and mean±SD for continuous variables. Pearson's Chi-square test and Fisher's exact test were used to compare categorical variables. The Kaplan-Meier method was used to compare the OS and PFS durations between the various clinical parameter groups. Statistical significance was set at $p<0.05$.

RESULTS

In this study, 110 patients with metastatic disease at diagnosis or metastatic disease that recurred during the follow-up were screened. 91 the patients received first-line treatment. A total of 43 patients 25 (58.1%) males and 18 (41.9%) female received second-line treatment. The mean age was 55.86±11.6 years. Lung, liver, distant lymph node, and bone metastases were present in 69.8%, 34.8%, 30.2%, and 23.2% of patients, respectively. At the time of diagnosis, 72.1% of patients had metastatic disease. Among the patients who received second-line chemotherapy, 53.5% responded to first-line treatment. In contrast, 21% of the patients had a complete or partial response to second-line treatment and 32.6% had progressed. Grade 3-4 neutropenia developed in 18.6%, grade 3-4 thrombocytopenia in 14%, and neuropathy in 23.3%. The other demographic and clinical characteristics of the patients are summarized in **Table 1**. In the irinotecan-based chemotherapy regimen group, 15 and six patients received FOLFIRI and irinotecan, respectively. In the taxane-based chemotherapy regimen group, 17 and five patients received paclitaxel and docetaxel, respectively.

Considering all patients, the median PFS was 5 months (95% CI, 3.0 to 6.9) and the median OS was 7 months (95% CI, 4.5 to 9.5) (**Figure 1**). The median PFS was 4 months (95% CI, 2.9 to 5.0) in the irinotecan-based regimen group and 7 months (95%

Table 1. Demographic and clinical features of the patients

		Average±SD	Min-max (median)
Diagnosis age		55.86±11.6	26-83 (57)
		n	%
Gender	Male	25	58.1
	Female	18	41.9
Comorbidities			
Hypertension		8	18.6
Diabetes mellitus		4	9.3
Ischemic heart disease		5	11.6
Chronic obstructive lung disease		4	9.3
Smoking status		9	20.9
Dysphagia		42	97.7
Abdominal pain		6	14.0
Weight loss		21	48.8
Chemotherapy regimens	Irinotecan-based	21	48.8
	Taxane-based	22	51.2
ECOG	0	10	23.3
	1	29	67.4
	2	4	9.3
Localization of metastasis	Distant lymph node	13	30.2
	Lung	30	69.8
	Liver	15	34.8
	Bone	10	23.2
Diagnosis stage	Local/locally advanced	12	27.9
	Metastatic	31	72.1
Grade	1	2	4.7
	2	31	72.1
	3	10	23.2
Response to first-line treatment	Complete response	6	14
	Partial	17	39.5
	Stable	6	14
	Progression	14	32.6
Advers events			
Neutropenia		8	18.6
Anemia		7	16.3
Thrombocytopenia		6	14.0
Febrile neutropenia		5	18.6
Mucositis		15	34.9
Diarrhea		13	30.2
Neuropathy		10	23.3
Nausea and vomiting		12	27.9
Response to second-line treatment	Complete response	2	4.7
	Partial	7	16.3
	Stable	20	46.5
	Progression	14	32.6
Progression	No	35	81.4
	Yes	8	18.6
Latest situation	Exitus	35	81.4
	Alive	8	18.6

SD: Standard deviation, Min: Minimum, Max: Maximum, ECOG: Eastern Cooperative Oncology Group

CI, 4.8 to 9.1) in the taxane-based regimen group (p=0.80). The median OS was 5 months (95% CI, 2.5 to 7.4) in the irinotecan-based regimen group and 10 months (95% CI, 2.6 to 17.3) in the taxane-based regimen group (p=0.122) (**Figure 2**). Among the side effects between regimens, grade 3-4 neutropenia (p=0.046) and grade 3-4 neuropathy (p=0.034) were higher in the taxane-based regimen group, while grade 3-4 mucositis (p=0.027) was higher in the irinotecan-based regimen group. There were no statistically significant differences in the other side effects (**Table 2**).

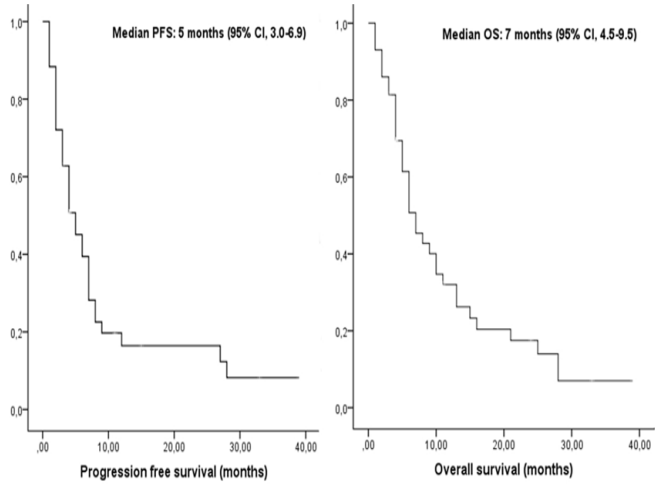

Figure 1. The overall survival and progression-free survival of the patients

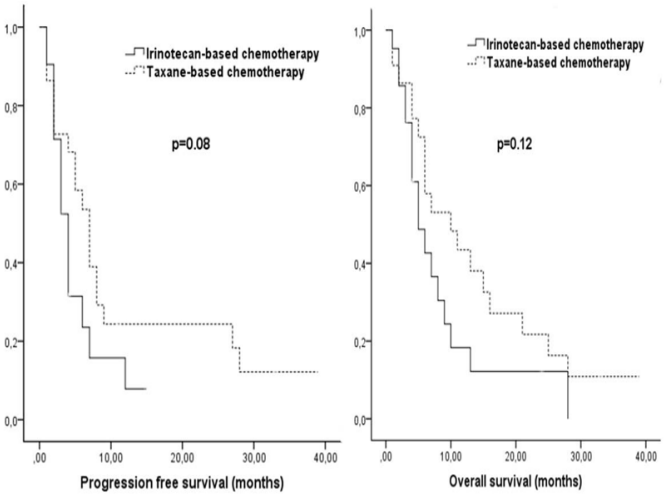

Figure 2. The overall survival and progression-free survival results according to the chemotherapy regimens

Table 2. Comparison of side effects of chemotherapy regimens

	Chemotherapy regimens				
	Irinotecan-based		Taxane-based		
	n (21)	%	n (22)	%	p
Grade 3-4 neutropenia	1	4.8	7	31.8	0.046
Grade 3-4 anemia	3	14.2	4	18.2	1.000
Grade 3-4 thrombocytopenia	2	9.5	4	18.2	0.664
Febrile neutropenia	2	9.5	6	27.2	0.240
Grade 3-4 mucositis	11	52.4	4	18.2	0.027
Grade 3-4 diarrhea	9	42.9	4	18.2	0.104
Grade 3-4 neuropathy	2	9.5	8	36.4	0.034
Grade 3-4 nausea and vomiting	8	12.1	4	18.2	0.185

DISCUSSION

In our study, we found no statistically significant differences in the median PFS and median OS between the two different chemotherapy groups used in the second-line treatment of patients with metastatic esophageal SCC. Among the side effects, grade 3-4 neutropenia and grade 3-4 neuropathy were higher in the group receiving taxane-based regimens, while grade 3-4 mucositis was higher in the group receiving irinotecan-based regimens.

A meta-analysis published in 2017 that investigated the efficacy of palliative treatment for metastatic esophageal cancer showed that second-line treatment contributed to OS.[16] Although the response of patients to second-line treatment varies, in a retrospective study evaluating paclitaxel and docetaxel regimens, docetaxel had a response rate of 5.3% and paclitaxel 19.4%.[17] In a phase-2 study evaluating 53 patients with progressive esophageal cancer who had previously received platinum-based chemotherapy and weekly paclitaxel, the response rate was 44.2%.[9] In a phase-3 study comparing camrelizumab with classical chemotherapy, the response rate was 7% in the classical chemotherapy arm.[14] In this study, the response rate was 21%.

In a meta-analysis of 29 studies evaluating second-line treatment for esophageal cancer published between 1996 and 2011, the time to progression was found to be between 1.4 and 6.2 months. Approximately 40% of patients with disease progression after first-line chemotherapy progress to second-line treatment.[18] Similarly, in our study, the median PFS was 5 months and 47.2% of patients who received first-line treatment were able to receive second-line treatment.

In a retrospective study evaluating patients using taxane and non-taxane chemotherapy regimens, the median OS was 7.4 months in the group receiving taxane-based regimens and 5.1 months in the group receiving non-taxane-based regimens and was found to be statistically significant.[19] In a study evaluating 124 patients who had previously received platinum-based chemotherapy and developed disease progression, the median OS was 6.1 months for those receiving docataxel and 7.2 months for those receiving paclitaxel.[20] In a retrospective study evaluating dual chemotherapy agents (FOLFIRI, carboplatin-paclitaxel and cisplatin-5-fluorouracil) as second-line treatments for metastatic esophageal SCC, the median OS was 14 months.[21] In a phase-3 study comparing nivolumab treatment with taxane agents, the median OS in the chemotherapy arm was 8.4 months.[13] In our study, the median OS was seven months for all patients, 10 months for the taxane-based regimen group, and five months for the irinotecan-based regimen group. Although the OS in the taxane group was twice that of the irinotecan group, the difference was not statistically significant owing to the limited number of patients.

In a retrospective study comparing docetaxel and paclitaxel after platinum-based therapy, grade 3-4 neutropenia was found in 40.3%, grade 3-4 anemia in 3.4% and grade 3-4 neuropathy in none.[20] In a study involving 163 patients evaluating taxane group chemotherapies as second-line treatment, grade 3-4 neutropenia was seen in 32.6%, grade 3-4 anemia in 9.1% and grade 3-4 thrombocytopenia in 2.3% in the docetaxel group, while grade 3-4 neutropenia was seen in 16.1% and grade 3-4 neuropathy in 6.5% in the paclitaxel group. Grade 3-4 anemia and grade 3-4 thrombocytopenia were not observed in the paclitaxel group.[17] In a study evaluating 53 patients who had previously received platinum-based chemotherapy and progressed, the most common grade 3-4 side effects were neutropenia (52.8%) and leukopenia (45.3%).[9] In a study comparing tislelizumab with classical chemotherapy, 55.8% of patients in the classical chemotherapy cohort developed grade 3 or higher side effects.[15]

In our study, 18.6% of patients developed grade 3-4 neutropenia, 14% grade 3-4 thrombocytopenia, and 23.3% developed neuropathy. As expected, grade 3-4 neutropenia and grade 3-4 neuropathy were higher in the group receiving the taxane-based regimen, while grade 3-4 mucositis was higher in the group receiving irinotecan-based regimens.

Limitations

Although our study has limitations, such as its retrospective and single-center nature, it is one of the few studies performed in this patient group in recent years and is important because it reflects our clinical practice. In the present study, the limited sample size may have impacted the frequency of adverse effects observed. However, the retrospective nature of the study also raises the possibility that the clinician may not have asked enough questions about side effects. Thus, it is suggested that a multicenter prospective cohort study with an expanded sample size might yield advantageous outcomes.

CONCLUSION

As a result, although taxane-group chemotherapeutic agents increased the frequency of neutropenia and neuropathy in the second-line treatment of patients with esophageal SCC, they increased OS compared to irinotecan-containing agents. For patients who do not receive taxane group agents as first-line treatment, we believe that taxane group chemotherapeutic agents should be used as second-line treatment, rather than irinotecan-based treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2023, Decision No: 2023/09-01).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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