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Clinical Trial Results

Single-Agent Versus Double-Agent Chemotherapy in Concurrent Chemoradiotherapy for Esophageal Squamous Cell Carcinoma: Prospective, Randomized, Multicenter Phase II Clinical Trial

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Key Words. Chemoradiotherapy • Esophageal squamous cell carcinoma • Lymphopenia • Esophageal cancer • Fluoropyrimidine S-1 • Cisplatin

Trial Information

- **ClinicalTrials.gov Identifier:** NCT02913066
- **Sponsors:** Mianyang Health Committee, Mianyang Science and Technology Bureau, Sichuan Medical Association, Sichuan Health Committee
- **Principal Investigator:** Xiaobo Du
- **IRB Approved:** Yes

Lessons Learned

- The efficacy of single-agent chemotherapy was not significantly different from that of double-agent chemotherapy in concurrent chemoradiotherapy for inoperable esophageal squamous cell carcinoma.
- Single-agent concurrent chemoradiotherapy had lower gastrointestinal and hematologic toxicity.
- Overall survival and progression-free survival were not significantly different between single- and double-agent concurrent chemoradiotherapy.

Abstract

Background. This multicenter, randomized, phase II trial aimed to compare the efficacy and safety of single-agent concurrent chemoradiotherapy using the oral fluoropyrimidine S-1 with those of double-agent concurrent chemoradiotherapy using S-1 and cisplatin in patients with inoperable esophageal squamous cell carcinoma.

Methods. Patients with inoperable esophageal squamous cell carcinoma (clinical stages I to III) were randomly allocated to the single-agent group (S-1) or the double-agent group (S-1/cisplatin). The concurrent intensity-modulated radiation therapy plan was similar for both groups: planning target volume 1.8 Gy/f*30–33f and planning gross target volume of 2 Gy/f*30–33f. The primary outcome measure was the endoscopic complete response rate.

Results. Of the 105 patients randomized, 89 were assessable. The endoscopic complete response rate was 46.9% (23/49) in the single-agent group and 52.5% (21/40) in double-agent group. The median progression-free survival within a median follow-up of 23 months was 20 and 21 months, respectively. The median overall survival was 26 months and not reached, respectively. Grade 3 hematological toxicities occurred in 4.1% and 27.5% of the patients in the single- and the double-agent group, respectively.

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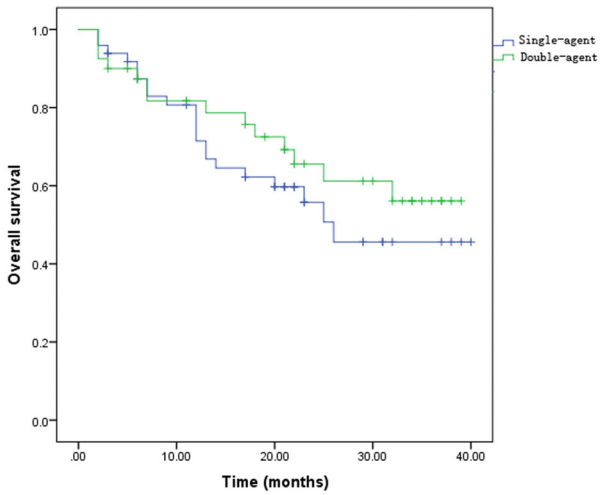

Figure 1. Kaplan-Meier analysis of overall survival (OS). The median follow-up period was 23 months. There was no significant difference in OS (median, 26 months vs. not reached; p = .367) between the single-agent group and the double-agent group.

Conclusion. Single-agent chemotherapy in concurrent chemoradiotherapy for inoperable esophageal squamous cell carcinoma has good efficacy and safety, thus warranting a phase III trial. ***The Oncologist*** 2020;25:e1900–e1908

Discussion

Previous studies showed that concurrent chemoradiotherapy for esophageal cancer yields a complete response (CR) rate of 50%–65%. In the current study, we found a CR rate of 46.9% and 52.5% for single- and double-agent chemotherapy, respectively, whereas the partial response (PR) rate was 30.7% and 20%. The overall response rate and the CR are similar to those previously reported. Although the CR rate of the double-agent group was slightly higher, the difference was not significant. There was also no significant difference in overall response rate between the two groups.

To our best knowledge, only two retrospective studies have compared the progression-free survival (PFS) and overall survival (OS) between single-agent concurrent chemoradiotherapy and double-agent concurrent chemoradiotherapy for esophageal cancer. Our previous multicenter retrospective analysis found a lower 5-year PFS and OS in the single-agent group compared with the double-agent group (40.9% vs. 52.5% and 60.7% vs. 78.2%, respectively), but there was no significant difference (p = .367 and .161, respectively). The shortened survival in the single-agent group may be attributed to the relatively older age in this group compared with the double-agent group (62.75 $\pm$ 7.8 years vs. 58.32 $\pm$ 9.17 years, respectively). Another retrospective single-institution study reported 5-year OS rates of 44.3% and 27.4% for the single-agent group and the double-agent group (p < .05), respectively, and chemotherapy regimen was the only factor associated with OS. In this study, the median OS of the single-agent group was 26 months, whereas that of the double-agent group was not reached (Fig. 1). The median PFS of the single-agent group was 20 months, whereas that of the double-agent group was 21 months. These OS and PFS rates were consistent with those previously reported. In contrast to the prolonged survival in the double-agent group in previous studies, we found no significant difference between the single-agent group and the double-agent group in this study, indicating the need for a phase III trial to further determine the long-term effect of single- and double-agent concurrent chemoradiotherapy.

We found higher rates of grade 2 vomiting and grade 2 and 3 anemia and thrombocytopenia in the double-agent group, which could be possible because cisplatin is highly likely to cause vomiting. Furthermore, previous retrospective studies showed that single-agent concurrent chemoradiotherapy has lower hematotoxicity than double-drug concurrent chemoradiotherapy in patients with esophageal cancer. There was no significant difference in the rates of radiation esophagitis and radiation pneumonia between the two groups. This could be because cisplatin does not aggravate esophageal and pulmonary injury, and there was no significant difference in the radiotherapy dose between the two groups.

In summary, the efficacy of single-agent chemotherapy is not significantly different from that of double-agent chemotherapy in concurrent chemoradiotherapy for inoperable esophageal squamous cell carcinoma. Furthermore, it has lower gastrointestinal and hematological toxicity. There was also no significant difference in OS and PFS between the two regimens. Future phase III trials comparing the same regimens are needed.

Trial Information	
Disease	Esophageal cancer
Stage of Disease/Treatment	Primary
Prior Therapy	Two prior regimens
Type of Study	Phase II, randomized
Primary Endpoint	Complete response rate
Secondary Endpoints	Overall survival, progression-free survival, toxicity
Additional Details of Endpoints or Study Design	
Study design and patients: This was a prospective, randomized, controlled, multicenter phase II clinical trial to test the feasibility of the single-agent regimen (S-1) versus the double-agent regimen (S-1/cisplatin) in patients with esophageal squamous cell carcinoma. Two conditions needed to be fulfilled before recommending a subsequent phase III trial of this question: the complete response rate of single-agent chemotherapy was not significantly different to that of double-agent chemotherapy, and OS and PFS are not significantly different between the single-agent group and the double-agent group.	

The study was approved by the Ethics Committee of Mianyang Hospital (approval no. S2016055) and was conducted according to the tenets of the Helsinki Declaration and its later amendments. All participants provided written informed consent form prior to participation. The study was registered at ClinicalTrials.gov (registration no. NCT02913066), and its detailed rationale and methods have been published elsewhere. Briefly, we enrolled patients with confirmed stages I to III esophageal squamous cell carcinoma from any of the nine hospitals in Sichuan province. The eligibility criteria were (a) age 18 to 75 years; (b) inoperable esophageal squamous cell carcinoma or refusal of surgery; (c) Eastern Cooperative Oncology Group status 0–2; (d) without esophageal perforation, active esophagorrhagia, or apparent trachea or thoracic macrovascular invasion; (e) no history of chest chemotherapy and radiotherapy, immunological therapy, or biotherapy; and (f) with the lower bound of primary esophageal lesions more than 3 cm away from the junction between the esophagus and the stomach.

Treatment: Eligible patients were randomly allocated in a 1:1 ratio to the single-agent concurrent chemoradiotherapy group or the double-agent concurrent chemoradiotherapy group by a central randomization center. Single-agent chemotherapy comprised S-1 (Lunan Pharmaceutical Group, Shandong, China) 70 mg/m^2 from Monday to Friday until the end of radiotherapy. Double-agent chemotherapy comprised S-1 70 mg/m^2 for the first 14 days and from the 22nd day to the 35th day and cisplatin (Jiangsu Haosen Pharmaceutical Co., Ltd, Jiangsu, China) 25 mg/m^2 for the first 3 days and from the 22nd day to the 24th day. Two cycles of adjuvant chemotherapy, followed by radiotherapy, were given for both groups. The intensity-modulated radiation therapy plan was similar for both groups, as follows: planning target volume of 1.8 Gy/f*30–33f and planning gross target volume of 2 Gy/f*30–33f.

Outcome measures: The primary outcome measure was the endoscopic complete response rate evaluated within 3 months after the end of the treatment. Endoscopic complete response rate was defined as the complete disappearance of any tumor ulceration or stenosis with no new lesion (all endoscopic images and reports had to be available) in the entire esophagus and no evidence of progression on computed tomography. Biopsies were not mandatory. Tumor response was assessed during week 15 according to RECIST. The secondary outcome measures were toxicity, PFS, and OS.

Statistical analysis: Considering a two-sided test significance level of .05 and a power of 85%, the rate of loss to follow-up of the two groups was set to be 10%. Available data indicate that the complete response rate of esophageal carcinoma in the treatment group and the control group was 40% on average, and the lower confidence interval (CI) limit of 20% esophageal carcinoma complete response was excluded. As such, the calculated total sample size was 88 patients. The proportion of patients with clinical response and the 95% CI were calculated. The chi-square test and the Kaplan-Meier method were used to analyze the survival rates and severity of disease progression, respectively, and Fisher' exact (probability) test was used to analyze the correlations between clinical outcomes and toxicity. All statistical tests were performed using IBM SPSS Statistics version 24.0. All tests were two sided, and a value of $p < .05$ was considered to indicate statistical significance.

Investigator's Analysis	Active and should be pursued further

Drug Information: Control

Drug 1	
Generic/Working Name	S-1
Trade Name	S-1
Company Name	Lunan Pharmaceutical Group
Drug Type	Small molecule
Drug Class	Antimetabolite
Dose	70 milligrams (mg) per squared meter (m^2)
Route	Oral (p.o.)
Schedule of Administration	Daily for the first 14 days and from the 22nd day to the 35th day, 56th day to the 69th day, 77th day to the 90th day.
Drug 2	
Generic/Working Name	Cisplatin
Trade Name	Cisplatin
Company Name	Jiangsu Haosen Pharmaceutical Co., Ltd
Drug Type	Small molecule
Drug Class	Alkylating agent
Dose	25 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Daily ×3 for the first 3 days and from the 22nd day to the 24th day, 56th day to the 58th day, 77th day to the 79th day.

Drug Information: Experimental	
Drug 1	
Generic/Working Name	S-1
Trade Name	S-1
Company Name	Lunan Pharmaceutical Group
Drug Type	Small molecule
Drug Class	Antimetabolite
Dose	70 milligrams (mg) per squared meter (m^2)
Route	Oral (p.o.)
Schedule of Administration	From Monday to Friday until the end of radiotherapy, and from the 56th day to the 69th day, 77th day to the 90th day.

Patient Characteristics: Control	
Number of Patients, Male	34
Number of Patients, Female	6
Stage	TNM classification, *n* (%)
	I: 5 (12.5)
	II: 20 (50.0)
	III: 15 (37.5)
Age	Median (range): 64 years (48–73 years)
Number of Prior Systemic Therapies	Median: 0
Performance Status: ECOG	0 — 9
	1 — 29
	2 — 2
	3 —
	Unknown —
Tumor characteristics	*n* (%)
Location of primary tumor	
Cervical	5 (12.5)
Upper thoracic	17 (42.5)
Middle thoracic	16 (40.0)
Lower thoracic	2 (5)
Inoperability	
Carcinologic reason	36 (90.0)
Therapeutic/patient choice	4 (10.0)
Weight loss	
<10%	37 (92.5)
≥10%	3 (7.5)
Tumor length, median (range), mm	3 (20–200)
Cancer Types or Histologic Subtypes	Squamous cell carcinoma, 40

Patient Characteristics: Experimental	
Number of Patients, Male	36
Number of Patients, Female	13
Stage	TNM classification, *n* (%)
	I: 4 (8.2)
	II: 31 (63.2)
	III: 14 (28.6)

Age	Median (range): 64 years (48–75 years)
Number of Prior Systemic Therapies	Median: 0
Performance Status: ECOG	0 — 10 1 — 38 2 — 1 3 — Unknown —
Tumor characteristics	*n* (%)
Location of primay tumor	
Cervical	2 (4.1)
Upper thoracic	18 (36.8)
Middle thoracic	23 (46.9)
Lower thoracic	6 (12.2)
Inoperability	
Carcinologic reason	35 (71.4)
Therapeutic/patient choice	14 (28.6)
Weight loss	
<10%	43 (87.8)
≥10%	6 (12.2)
Tumor length, median (range), mm	57 (30–105)
Cancer Types or Histologic Subtypes	Squamous cell carcinoma, 49

Primary Assessment Method: Control (Complete Response Rate)	
Number of Patients Screened	49
Number of Patients Enrolled	42
Number of Patients Evaluable for Toxicity	40
Number of Patients Evaluated for Efficacy	36
Evaluation Method	Esophagoscopy
Response Assessment CR	*n* = 21 (52.5%)
Response Assessment PR	*n* = 8 (20%)
Response Assessment SD	*n* = 4 (10%)
Response Assessment PD	*n* = 3 (7.5%)
Response Assessment OTHER	*n* = 4 (10%)
(Median) Duration Assessments PFS	21 months, CI: 95%
(Median) Duration Assessments OS	>26 months, CI: 95%

Outcome Notes

In total, 80 patients who completed the endoscopic follow-up were included in the endoscopic complete response rate analysis: 44 of 49 patients in the single-agent group and 36 of 40 patients in the double-agent group. The five patients in the single-agent group were excluded because of loss to follow-up (n = 1) and no endoscopic evaluation (n = 4). The four patients in the double-agent group were excluded because of loss to follow-up (n = 1) and no endoscopic evaluation (n = 3). Overall, 44 patients achieved endoscopic CR. There was no significant difference in the rate of endoscopic complete response between the single-agent group and the double-agent group (23 patients [46.9%] vs. 21 patients [52.5%], $p > .05$).

The median follow-up period was 23 months. There was no significant difference in OS (median, 26 months vs. not reached; $p = .367$) and PFS (median, 20 months; 95% CI, 12.8%–27.1% vs. median, 21 months; 95% CI, 16.1%–25.8%; $p = .387$) between the single-agent group and the double-agent group.

Primary Assessment Method: Experimental (Complete Response Rate)	
Number of Patients Screened	56
Number of Patients Enrolled	49
Number of Patients Evaluable for Toxicity	49
Number of Patients Evaluated for Efficacy	44
Evaluation Method	Esophagoscopy
Response Assessment CR	*n* = 23 (46.9%)
Response Assessment PR	*n* = 15 (30.7%)
Response Assessment SD	*n* = 3 (6.1%)
Response Assessment PD	*n* = 3 (6.1%)
Response Assessment OTHER	*n* = 5 (10.2%)
(Median) Duration Assessments PFS	20 months, CI: 95%
(Median) Duration Assessments OS	26 months, CI: 95%

Outcome Notes

In total, 80 patients who completed the endoscopic follow-up were included in the endoscopic complete response rate analysis: 44 of 49 patients in the single-agent group and 36 of 40 patients in the double-agent group. The five patients in the single-agent group were excluded because of loss to follow-up (n = 1) and no endoscopic evaluation (n = 4). The four patients in the double-agent group were excluded because of loss to follow-up (n = 1) and no endoscopic evaluation (n = 3). Overall, 44 patients achieved endoscopic CR. There was no significant difference in the rate of endoscopic complete response between the single-agent group and the double-agent group (23 patients [46.9%] vs. 21 patients [52.5%], $p > .05$).

The median follow-up period was 23 months. There was no significant difference in OS (median, 26 months vs. not reached; $p = .367$) and PFS (median, 20 months; 95% CI, 12.8%–27.1% vs. median, 21 months; 95% CI, 16.1%–25.8%; $p = .387$) between the single-agent group and the double-agent group.

Adverse Events: Control

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Vomiting	44	23	33	0	0	0	56
Esophagitis	19	13	60	5	3	0	81
Pneumonitis	72	10	18	0	0	0	28
White blood cell decreased	53	7	26	14	0	0	47
Anemia	46	23	28	3	0	0	54
Platelet count decreased	56	18	13	13	0	0	44

Adverse Events Legend
Adverse events occurring in >20% of patients
Abbreviation: NC/NA, no change from baseline/no adverse event.

Adverse Events: Experimental

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Vomiting	78	12	10	0	0	0	22
Esophagitis	21	18	57	2	2	0	79
Pneumonitis	82	4	12	2	0	0	18
White blood cell decreased	47	20	29	4	0	0	53
Anemia	76	18	6	0	0	0	24
Platelet count decreased	88	6	6	0	0	0	12

Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Esophageal cancer is the ninth most common malignancy worldwide, with approximately 572,034 incident cases worldwide annually [1]. Esophageal cancer is also the sixth most common cause of cancer-related mortality. In China, esophageal cancer is the third most common malignancy [2] and the fourth most common cause of cancer-related death. A 2015 epidemiological investigation found that the number of esophageal cancer cases in China accounts for more than 50% of the total cases worldwide, with 477,900 new cases and 375,000 related deaths annually [3, 4]. Of these, more than 90% have esophageal squamous cell carcinoma [5].

The preferred treatment modality for esophageal cancer is surgery, but 80% of patients are no longer eligible for radical surgery upon diagnosis [6, 7]. These patients are thus indicated for radiotherapy [8]. However, the 5-year survival rate of patients undergoing conventional radiotherapy is only 10% [9]. Concurrent chemoradiotherapy has been found to yield better overall survival than radiotherapy [10–12]. Thus, concurrent chemoradiotherapy has become the standard treatment modality for inoperable esophageal squamous cell carcinoma [13, 14].

Concurrent chemoradiotherapy for inoperable esophageal squamous cell carcinoma generally comprises a platinum-based or fluorouracil-based combination chemotherapy and intensity-modulated radiotherapy. However, previous retrospective studies have shown that only 9%–38.5% of patients with esophageal cancer receiving radiotherapy with concurrent 5-fluorouracil/cisplatin chemotherapy complete the treatment plan because of severe toxic effects [15, 16]. Compared with double-agent concurrent chemoradiotherapy, single-agent concurrent chemoradiotherapy has fewer side effects while having the same therapeutic benefit in several malignancies, including lung cancer, cervical cancer, and head and neck cancer. Thus, it is recommended as the standard treatment modality for those tumors [17–19]. Our previous retrospective study found that the effectiveness of single-agent concurrent chemoradiotherapy was not inferior to double-agent concurrent chemoradiotherapy but had lower toxicity for patients with unresectable esophageal squamous cell carcinoma [20]. Another study showed that single-agent concurrent chemoradiotherapy was superior to double-agent concurrent chemoradiotherapy [21]. However, no prospective randomized clinical trial has compared the efficacy and safety of single-agent concurrent chemoradiotherapy with those of double-agent concurrent chemoradiotherapy. Therefore, this study aimed to assess the efficacy and safety of single-agent chemotherapy and compare them with those of double-agent chemotherapy as part of concurrent chemoradiotherapy in patients with inoperable esophageal squamous cell carcinoma.

Previous studies showed that concurrent chemoradiotherapy for esophageal cancer yields a complete response (CR) rate of 50%–65% [22, 23]. A phase I study of 12 elderly patients with esophageal cancer receiving single-agent S-1 with concurrent radiotherapy reported a CR rate of 66.7% [24]. A phase II study on elderly patients with esophagus cancer reported that 22 patients with stage II to III disease received 50 Gy radiotherapy and cisplatin treatment concurrently, and the CR rate was 63.6% [25]. Jia et al. [26] evaluated lobaplatin combined with fluorouracil for concurrent chemoradiotherapy for inoperable esophagus cancer and found an overall response rate of 85.0% (51/60). In the current study, we found a CR rate of 46.9% and 52.5% for single-agent and double-agent chemotherapy, and the partial response rate was 30.7% and 20%, respectively. The overall response rate and the CR are similar to those previously reported. Although the CR rate of the single-agent group was slightly lower, the difference was not significant. There is also no significant difference in overall response rate between the two groups (Table 1).

To our best knowledge, only two retrospective studies have compared the progression-free survival (PFS) and overall survival (OS) between single-agent concurrent chemoradiotherapy and double-agent concurrent chemoradiotherapy for esophageal cancer. Our previous multicenter retrospective analysis found a lower 5-year PFS and OS in the single-agent group (40.9% vs. 52.5% and 60.7% vs. 78.2%, respectively) [20], but the difference was not statistically significant (p = .367 and .161, respectively). The shortened survival in the single-agent group may have been attributed to the relatively older age in this group compared with the double-agent group (62.75 ± 7.8 vs. 58.32 ± 9.17). Furthermore, only disease stage was associated with OS and PFS in the multivariable analysis. Another retrospective single-institution study reported 5-year OS rates of 44.3% and 27.4% for the single-agent group and double-agent group ($p < .05$), and chemotherapy regimen was the only factor associated with OS [21]. In the study presented here, the median OS of the single-agent group was 26 months, whereas that of the double-agent group was not reached (Fig. 1). The median PFS of the single-agent group was 20 months, whereas that of the double-agent group was 21 months. These OS and PFS rates were consistent with those previously reported [27, 28]. We found no significant difference between the single-agent group and the double-agent group in this study, indicating the need for a phase III trial to further determine the long-term effect of single- and double-agent concurrent chemoradiotherapy.

We found higher rates of grade 2 vomiting and grade 2 and 3 anemia and thrombocytopenia in the double-agent group. This finding is consistent with the known side effect profile, including cisplatin as a highly emetogenic agent. Furthermore, previous retrospective studies showed that single-drug concurrent chemoradiotherapy has lower hematotoxicity than a double-agent regimen concurrent chemoradiotherapy in patients with esophageal cancer [20, 21]. Furthermore, there was no significant difference in the rates of radiation esophagitis and radiation pneumonia between the two groups. This could be because cisplatin does not aggravate

esophageal and pulmonary injury, and there was no significant difference in the radiotherapy dose between the two groups. The overall incidence rate of hematotoxicity in this trial is relatively similar to that of previous studies [27–31], but that in the single-agent group is higher [24]. This is attributed to the long-term oral administration of S1 (from Monday to Friday for six consecutive weeks), which may have aggravated the toxicity.

In summary, the efficacy of single-agent chemotherapy is not significantly different from that of double-agent chemotherapy in concurrent chemoradiotherapy for inoperable esophageal squamous cell carcinoma. Furthermore, it has lower gastrointestinal and hematological toxicity. There was also no significant difference in OS and PFS between the two regimens. Further phase III trials comparing the same regimens are needed.

Disclosures

The authors indicated no financial relationships.

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Table

Table 1. Tumor response

Response	S-1 group (*n* = 49), *n* (%)	S-1/cisplatin group (*n* = 40), *n* (%)	*p* value
CR	23 (46.9)	21 (52.5)	.812
PR	15 (30.7)	8 (20.0)	
SD	3 (6.1)	4 (10.0)	
PD	3 (6.1)	3 (7.5)	
Not assessed	4 (8.2)	3 (7.5)	
Missing	1 (2.0)	1 (2.5)	

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.