Phase II Study of Definitive Chemoradiation Therapy Using S-1 for Esophageal Squamous Cell Carcinoma Patients — the ESO-Shanghai 7 Trial Protocol

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Study protocol

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Abstract

Background: Concurrent chemoradiotherapy (CCRT) is a standard treatment for inoperable locally advanced esophageal carcinoma. However, there exists a group of patients who are intolerable to intravenous chemotherapy for the old age or with serious comorbidities. S-1 is an oral fluorouracil derivative with well tolerance than 5-fluorouracil. The ESO-Shanghai 7 trial aimed to access the safety and efficacy of S-1 combined with radiotherapy for esophageal squamous cell carcinoma (ESCC) patients who are elderly or with serious comorbidities.

Methods: 105 ESCC patients with old age or serious comorbidities will be enrolled in this prospective, single-arm phase 2 clinical trial. Patients will receive S-1 orally at a dose of 40 mg (BSA $\leq$ 1.6 m^2) or 50 mg (BSA >1.6 m^2) twice daily for 28 days. The concurrent radiotherapy dose is 61.2 Gy delivered in 34 fractions. The primary endpoints are 3-yr local control and number and grade of participants with adverse events, and the secondary endpoint is overall survival.

Discussion: The aim of this phase 2 trial is to determine the tolerance and efficacy of S-1 concurrent with radiotherapy for ESCC patients with old age or serious comorbidities. A very promising 3-yr local control should beat least 60% from the clinical point of view.

Trial registration: ClinicalTrials.gov, NCT01831531. Registered 29 March 2013, https://clinicaltrials.gov/ct2/show/NCT01831531?term=NCT01831531&draw=2&rank=1

Background

Concurrent chemotherapy inhibits the micrometastasis and enhances the effect of radiotherapy by increasing DNA damage and decreases the DNA damage repair, blocking the tumor at the radio-sensitive G2/M phase of the cell cycle[1-3]. As a result, concurrent chemoradiotherapy (CCRT) has been proved to prolong the progression-free survival (PFS) and overall survival (OS) in lung cancer, esophageal carcinoma, and head and neck cancer et al using cisplatin, 5-fluorouracil (5-Fu), paclitaxel as traditional regimens[1-4].

The Radiation Therapy Oncology Group (RTOG) 8501 trial proved that 5-Fu/cisplatin combined with radiotherapy significantly improved OS, local control and metastasis control than radiotherapy alone, which set the 5-Fu/cisplatin a standard concurrent chemotherapy regimen in esophageal cancer patients[5]. However, there exists a subgroup of patients who are not tolerant to intravenous chemotherapy for the reasons of old age (> 75 years) or serious comorbidities. Exploring a new chemotherapy regimen with high efficacy and low toxicity is an urgent issue for this subgroup.

S-1 (tegafur-gimeracil-oteracil potassium) is an oral fluorouracil derivative with low toxicity which has beenproved to be noninferior in efficacy to infusional fluorouracil for gastric cancer[6]. Therefore, we aim to verify the safety and efficacy of definitive radiotherapy combined with S-1 alone in locally advanced

esophageal squamous cell carcinoma (ESCC) patients who reject or cannot tolerate intravenous chemotherapy.

S-1, an oral fluorouracil derivative with radiosensitizing effect

5-Fu has been already emerged as a promising clinical radiosensitizer, available in CCRT of many malignant tumors in affecting the progress of cell cycle and inhibiting radiation damage repair[7-9]. S-1 contains tegafur and two enzyme inhibitors, gimeracil and oteracil. Contained with these enzyme inhibitors, S-1 is able to prolong the effectiveness with less toxicity than 5-Fu[10-11]. S-1is also considered to have a radiosensitizing effect. An *in vitro* experiment conducted by Harada et al.[12]demonstrated that S-1 combined with radiotherapy significantly suppressed the growth of oral cancer B88 and HSG cells, and the radio sensitization ratio of S-1 to B88 cells reached up to 1.45. Further verification also showed that the tumor growth had obviously been stunted in mice receiving S-1 with radiotherapy than radiotherapy alone, suggesting that S-1 improved the radiation response. Another study by Nakata et al. [13]also reported slower tumor growth in S-1 with radiotherapy group compared to S-1 alone or radiation alone group in mice implanted with colon cancer cell DLD-1. The results displayed no significant change in expression of thymidylate synthase when S-1 or radiotherapy given as single treatments, but strong down-regulation when both combined. Similar conclusion came out in mice models with pancreatic tumors[14]. Radiotherapy combined with S-1 significantly inhibited tumor growth($p < 0.01$), while it failed to display the antitumor activity when combined with 5-Fu, indicating that S-1 did activate the radiosensitizing effect by gimeracil.

Briefly, S-1 can maintain high drug concentration in blood with less toxicity just orally, meanwhile enhance the radiotherapeutic gain. Nevertheless, there are few *in vivo* or *in vitro* studies that focus on the radiosensitization of S-1 in esophageal cancer cell lines.

S-1, a drug of CCRT for esophageal carcinoma in phase 2 trials

S-1 has been proved to be an effective agent in CCRT for gastric cancer. However, few investigations have done for S-1 used in CCRT for esophageal carcinoma. At ASCO 2007, Iwase et al.[15]showed the effectiveness and safety of S-1 concurrent with cisplatin and 30Gy radiotherapy for advanced esophageal carcinoma. Complete and partial remission rate was 78% and 22% respectively in stage II disease, while, 58% and 32% respectively in stage III disease. The 3-year OS was 100% in stage II disease, while, the 1-year and 3-year OS was 70% and 44% respectively in stage III disease. The most frequent adverse events were grade 3 (25%) and 4 (12%) neutropenia. No grade 3-4 nonhematological adverse events occurred, in which grade 2 nausea (20%), pain (12%), oral mucositis, and renal dysfunction (5% each) were most common. Similarly, Cho et al.[16] adopted the CCRT schedule of S-1 plus cisplatin concurrent with 54Gy radiotherapy. In total of 27 patients, an objective response rate was observed in 20 (74.1%) patients, and 76% (21/27) got improvement of dysphagia. The median PFS and OS was 10.6 and 23.0 months respectively in patients with stage II and III disease, while, 5.4 and 11.6 months respectively in patients with stage IV. The main hematological toxicity caused by S-1 was neutropenia, but no

neutropenic fever was observed. The major non-hematological toxicities were asthenia and vomiting (**Table 1**).

Thus, it's still unclear whether S-1 concurrent with radiotherapy is superior to radiotherapy alone in patients with locally advanced esophageal carcinoma who cannot tolerate intravenous chemotherapy for the old age or severe comorbidities. In this phase 2 clinical trial, we aim to assess the safety and efficacy of S-1 concurrent with radiotherapy in the treatment of ESCC patients and provide the evidence for further clinical application of S-1 in this subgroup of ESCC patients.

Methods/design

Patient Selection

To be eligible for this study, patient must fulfill all of the inclusion criteria (**Table 2**), and be excluded if matching any of the exclusion criteria (**Table 3**).

Patients would be asked to withdraw from the trial when they have (1) ≥ grade 4 allergic or severe adverse reactions, (2) progress in disease during treatment, (3) pregnancy; (4) shown reluctance of continuation, (4) any conditions for which investigators may prematurely terminate the trial.

Sample Size and Statistical analysis

A total sample size of 105 will be required for this phase 2 study. The Kaplan-Meier method and log-rank tests will be used to estimate the local control rate and OS. Cox regression will be used to estimate the hazard ratios. Data will be analyzed with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Treatment

The treatment schedule is outlined in **Figure 1**. Patients will receive S-1 combined with concurrent radiotherapy. S-1 is orally taken and begins on day 1, with the beginning of cycle 1 of radiotherapy.

According to the current clinical practice in China, radiotherapy is delivered with photons to a total dose of 61.2 Gy in 34 fractions, which is distributed in 5 days per week at 1.8 Gy/d[17]. In detail, S-1 will be orally taken half an hour after the breakfast and dinner, then radiotherapy will be delivered within 30-60 minutes after oral administration.

Radiotherapy

The intensity modulated radiation therapy (IMRT) based on a CT simulation planning system with 5 to 8-mm-thick scan slice throughout the cricoid cartilage and diaphragm (available in enlargement of scan range if necessary), which is delivered with photons at least 6 MV, is applied for this trial.

The gross tumor volume (GTV) is defined as all known involved field, consisting of visible esophageal tumor and metastatic lymph nodes based on the imaging of endoscopic ultrasound, esophageal

radiography or CT scan (whichever is larger). The metastatic lymph nodes shall meet at least one of the following conditions: pathologic confirmation or short axis of ≥10 mm in the mediastinum or cervix, short axis of ≥5 mm at tracheoesophageal groove, or histologically proven metastatic via puncture.

The clinical target volume (CTV) includes the GTV as well as the superior-inferior regions 3cmbeyondthe primary tumor along the esophagus. The lateral, anterior and posterior borders of CTV are the same as GTV.

The planning target volume (PTV) is defined as a further 1 cm expansion added to the superior, inferior, anterior, posterior and lateral borders of CTV. The field next to the spinal cord can be slightly modified for less radiation exposure to the spinal cord.

Tissue inhomogeneity correction is adopted and suggests that 95% of the PTV receive ≥99% of the prescribed dose; 99% of the PTV receive ≥95% of the prescribed dose; <2 cm^3 of the PTV receive ≥120% of the prescribed dose; <1 cm^3 of the PTV receive ≥110% of the prescribed dose. The highest and lowest dose points inside the PTV need to be recorded.

Doses for critical organs delineated on all slices of the planning CT should be restricted to some degree. In the treatment plan, the spinal cord will be contoured on every CT slice and the margin of vertebra tube can be regarded as risk volume. The heart contours should begin at the level of the right atrium and right ventricle (pulmonary artery trunk, ascending main aorta and superior vena cava are excluded) and extend to the apex of the heart. The margin of both lungs can be contoured by automatic tools built in the system, but trachea and bronchia must be contoured manually and be excluded. The priority order of critical organ dose restrictions in details is as follows:

1. Spinal cord: The max dose point must be less than 45 Gy, and cannot be exceeded for any reason.
2. Lungs: The lung volume (PTV excluded) receiving 20 Gy must be equal to or less than 30% of the total lung volume, and the mean lung dose must be equal to or less than 15 Gy.
3. Heart: The mean dose must be less than 40Gy.

Dose Modifications

By principle, all participants should receive the required dose as enough as possible during the trial. Though, in some conditions, modifications of treatment dose can be taken into consideration.

Chemotherapy Dose modifications and interruption

First of all, chemotherapy dose modifications are strictly limited to twice at most and chemotherapy delay 2 weeks at most, otherwise, chemotherapy will be terminated.

If any following situation is observed during the trial, chemotherapy modification should be based on the details in adherence to the minimum dose administration in co-occurrence of several toxicities.

Hematological toxicity

Chemotherapy should be stopped and delayed when participants suffer from either ANC <1.5×10^9 /L or PLT <80×10^9 /L. If necessary, the chemotherapy dose should be modified according to the lowest counts of blood cells in the previous cycle (**Table 4**).

Non-hematological toxicity

The patient will continue to get chemotherapy after recovery from ≥ grade 3 non-hematological toxicities (except neurotoxicity and nephrotoxicity) and satisfaction to ≤ grade 2 CTCAE. S-1 dose should be modified as follows: daily dose reduces from 100 mg to 80 mg or 80 mg to 60 mg when ≥ grade 3 non-hematological toxicities (except neurotoxicity and nephrotoxicity) occurred.

Radiotherapy Dose modifications and interruption

Logically, the normal organ dose constraints should not be exceeded. If the dose has to exceed the constraint value in order to achieve adequate coverage of PTV, some modifications are taken into consideration by investigators, or the patient has to be excluded from the trial. The acceptable violations are as follows: 92–95% of the PTV is able to receive ≥99% of the prescribed dose; the critical organ dose restrictions can exceed 5%–10%, except the spinal cord where dose should be strictly controlled under 45Gy.

If following toxicity is observed, radiotherapy has to be delayed until toxicity is no more than grade 2. Besides, it is allowed to suspend at most 2 weeks or radiotherapy will be terminated.

- WBC <2.0 ×10^9 /L or ANC <1.0 ×10^9 /L
- PLT <50 ×10^9 /L
- Grade 4 or higher non-hematological toxicity

Observed adverse events during the study are evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) V4.0[18]. When adverse reactions such as leukopenia, vomiting occur, symptomatic drugs can be given concomitantly to relieve discomfort. All concomitant medications should be recorded. No other drugs related to tumor treatment (including other chemotherapy drugs, thymosin et al.) can be used during the trial.

Assessment of the endpoints

The primary endpoint is 3-yr local control rate and the number and grade of participants with adverse events according to the CTCAE V4.0. It's necessary to take esophagoscopy or fine-needle aspiration of superficial lymph node for pathological diagnosis to prove relapse. The local control time is from the start of treatment (day 1) to the date when the measurable new local recurrence, including the primary tumor and regional lymph node, is first observed. For patients who die of any other cause before the failure of

local control are recorded, the local control time will be defined as the time from day 1 to death. Patients who do not experience local control failure or death in the end will use the time of the last tumor assessment as the endpoint. Death is the second endpoint in this study and can be quantified by OS, which refers to the time from day 1 to death for any reason. When a patient is lost to follow-up, OS is up to the last recorded time of the contact with the patient. For patients who are still alive at the time of the last collection, the last contact time is used as the survival time. All patients will be followed up every 3 months for first 2 years and every 6 months after 2 years until death, loss of follow-up, or study termination for survival analysis and subsequent treatment.

Discussion

Concurrent chemoradiotherapy has become the standard treatment for inoperable locally advanced esophageal cancer patients[5]. However, the optimal evidence-based management for the subsets of esophageal cancer patients who are elderly or have serious medical comorbidities is currently lacking. S-1 based regimen combined with radiotherapy has showed moderate toxicities and promising response rates in esophageal cancer patients[16, 19]. Based on these evidences, we aim to determine the safety and efficacy of S-1 combined with radiotherapy in ESCC patients who reject or cannot tolerate intravenous chemotherapy due to old age or serious medical comorbidities in this phase 2 trial. There are some limitations existing in this study. First, we did not set the control arm of radiotherapy alone for comparison, and a randomized controlled study would be ideal. Second, there is no quality-of-life assessment applied in this study, which may provide more information of the treatment.

Abbreviations

CCRT: concurrent chemoradiotherapy; ESCC: esophageal squamous cell carcinoma; PFS: progression-free survival; OS: overall survival; CR: complete remission; PR: partial remission; SR: survival rate; 5-Fu: 5-fluorouracil; RTOG: Radiation Therapy Oncology Group; ULN: upper limit of normal; IMRT: intensity modulated radiation therapy; GTV: gross tumor volume; CTV: clinical target volume; PTV: planning target volume; PLT: platelet; ANC: absolute neutrophil count(s); CTCAE: common terminology criteria for adverse events; ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer; AIDS: acquired immunodeficiency syndrome.

Declarations

Acknowledgments

Not applicable.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions

KZ and YC planned the study. YC, KZ, GJ, HQ, XF, MF, KW, HY, HC, JX, YZ, HL, JZ, JC, XW, and JW are conducting the study. KZ and YC are responsible for the patient recruitment. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This trial has been approved by the Ethics Committee of Fudan University Shanghai Cancer Center(ID: ES02013-01).

Consent for publication

Not applicable.

Competing interests

None declared.

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Tables

Table 1
Results of Phase 2 clinical trials of S-1 in esophageal cancer.

Authors	Cases	Radiation dose (Gy)	Chemotherapy	Stage II CR/PR Rate	Stage III CR/PR Rate	Stage II/III 3-year SR	Stage IV PFS/OS
Iwase'et al.[15]	59	60	S-1 80 mg/m^2/d p.o bid *14d + cisplatin 70 mg/m^2 d8 q4w	78%/22%	58%/32%	100%/44%	-
Cho'et al.[16]	27	54	S-1 70 mg/m^2/d p.o bid *14d + cisplatin 70 mg/m^2 d1 q3w	70.6%/17.6%		-	5.4 ± 1.6/11.6 ± 1.6

Abbreviations: *CR* complete remission, *PR* partial remission, *SR* survival rate, *PFS* progression free-survival, *OS* overall survival

Table 2
Inclusion Criteria

1. Joined the study voluntarily and signed informed consent form
2. Histologically confirmed esophageal squamous cell carcinoma.
3. Aged > 75 years, or aged 18–75 years who refused intravenous chemotherapy, or intolerant to intravenous chemotherapy due to severe comorbidities such as severe liver or renal dysfunction, severe immunodeficiency, severe abnormal hematopoietic, severe cardiac or pulmonary diseases et al.
4. Local advanced esophageal squamous cell carcinoma (T2-4N0-1M0-1a, TxN1M0-1a, or TxNxM1a, AJCC 6th) with no radiotherapy for esophageal carcinoma prior to enrollment.
5. Adequate organ functions for chemoradiation therapy: (1) white cell count ≥ 3×10^9/L; (2) hemoglobin ≥ 9 g/dL; (3) absolute neutrophil counts ≥ 1.5×10^9/L; (4) platelet counts ≥ 70×10^9/L; (5) total bilirubin < 1.5 upper limit of normal (ULN); (6) the ratio of aspartate transaminase to alanine aminotransferase ≤ 2.5 ULN; and (7) creatinine ≤ 1.5 ULN.
6. ECOG performance status of 0–2.
7. Life expectancy ≥ 3 months, based on the judgement of doctors.
8. Use of an effective contraceptive for adults to prevent pregnancy.

Table 3
Exclusion Criteria

1. Complete esophageal obstruction, deep esophageal ulcer, esophageal perforation, or hematemesis.
2. History of radiotherapy or chemotherapy for esophageal cancer.
3. History of surgery within 28 days before Day 1.
4. History of prior malignancies (other than skin basal cell carcinoma or cervical carcinoma in situ with a disease-free survival of at least 3 years).
5. Participation in other interventional clinical trials within 30 days.
6. Pregnant or breast-feeding women or fertile patients who refused to use contraceptives.
7. Drug addiction, alcoholism or AIDS diagnosis.
8. Uncontrolled seizures or psychiatric disorders.
9. Patients with metastatic disease i.e. M1b according to AJCC 2002.
10. Other ineligible conditions according to researchers.

Table 4
S-1 dose modifications when hematological toxicity occurs.

PLT(10^9/L)		ANC(10^9/L)	S-1 dose
≥ 50	AND	≥ 0.5	100%
≥ 50	AND	< 0.5	daily dose reduces from 100 mg to 80 mg or 80 mg to 60 mg
< 50	AND	Any count	daily dose reduces from 100 mg to 80 mg or 80 mg to 60 mg
Abbreviations: *PLT* platelet, *ANC* absolute neutrophil count(s).			

Figures

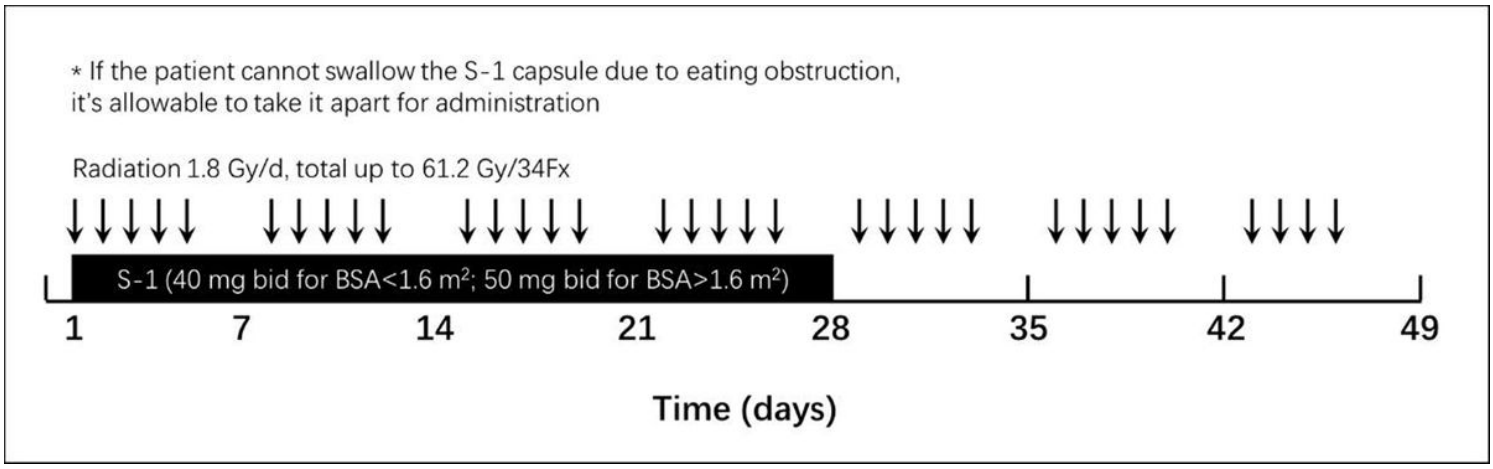

Figure 1

S-1 is administered orally at a dose of 40 mg (BSA ≤ 1.6 m2) or 50 mg (BSA >1.6 m2) twice daily from day1 to day 28, with the beginning of radiotherapy. Radiotherapy is delivered with photons in 34 fractions to a total dose of 61.2 Gy, which is distributed in 5 days per week at 1.8 Gy/d.