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FULL PAPER

Phase I study of concurrent selective lymph node late-course accelerated hyperfractionated radiotherapy and S-1 plus cisplatin for locally advanced oesophageal squamous cell carcinoma

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Objective: This Phase I study aimed to assess the safety and efficacy of concurrent selective lymph node (SLN) late-course accelerated hyperfractionated (LCAF) intensity-modulated radiotherapy (IMRT) and S-1 plus cisplatin (CDDP) for the locally advanced oesophageal squamous-cell carcinoma (ESCC).

Methods: The total dose of SLN LCAF IMRT was 59.6 Gy/34 fractions in 5.4 weeks. The concurrent chemotherapy (CCRT) was administered as follows: CDDP 25 mg m⁻² on Days 1–3 and Days 22–24; S-1 was applied in a de-escalating dosage with a decrement of 10 mg m⁻² per day, from its full dose level of 80 mg m⁻², orally twice daily on Days 1–14 and Days 22–35. We inferred the maximum-tolerated dose (MTD), dose-limiting toxicities (DLTs) and recommended dose, according to adverse reaction during CCRT.

Results: Totally, 15 patients with ESCC with T2–4N0–1M0–1a were enrolled in Dose Level 1 (80 mg m⁻²). In the initial five patients, two patients developed DLTs. As MTD was

not reached, five additional patients were treated with the same dose level, and DLTs occurred in only one patient. Similar results were found in the last five patients. After CCRT, the objective response rates were 100% for primary tumours and 86.2% for metastatic lymph nodes, respectively. Totally, the observed Grade 3 toxicities during CCRT were leukopenia (20%), neutropenia (20%) and dermatitis (13.3%), and no Grade 4 toxicity occurred. The Kaplan–Meier-estimated overall and progression survival rates were 86.7% and 66.7% (1 year), 73.3% and 60% (2 years) and 73.3% and 60% (3 years).

Conclusion: The concurrent SLN LCAF IMRT and chemotherapy with S-1 and CDDP was well tolerated and showed promising efficacy. The dose of S-1 in this regimen was recommended with 80 mg m⁻² orally twice daily on Days 1–14 and Days 22–35.

Advances in knowledge: CCRT with S-1 plus CDDP exhibited encouraging results with milder toxicities, high objective response rates and ideal overall survival time.

INTRODUCTION

Oesophageal cancer (EC) is the eighth most common cancer and the sixth leading cause of cancer-related death worldwide.¹ More than 90% of patients with EC are those with squamous-cell carcinoma in China. Although some significant improvements have been achieved in the treatments, their outcome remains poor, with 5-year survival of 19% during the period 2001–2007.²

Concurrent chemoradiotherapy (CCRT) has been recognized as the standard approach for patients with locally

advanced oesophageal squamous-cell carcinoma (ESCC), which leads to 55% of 2-year local control rate and approximately 27% (6–37%) of 5-year survival rate.^{3–6} As we know, in China, late-course accelerated hyperfractionated radiotherapy (LCAF RT) is widely utilized, as it can shorten the hospitalization time and decrease the possibility of tumour-cell regeneration during treatment. Furthermore, it significantly improves the local control rate and survival in ESCC, and the acute side effects can be tolerated without increase in long-term damage.⁷ In China, a randomized study of LCAF RT for patients with ESCC yielded very

encouraging results, which showed that the 5-year overall survival (OS) rate (34% vs 15%) and local control rate (55% vs 21%) were significantly higher in the LCAF RT group than in the conventional fractionation group.⁸ Since then, several results from retrospective and randomized studies have revealed similar conclusions.^{9–13} Three recent independent meta-analyses from China demonstrated the therapeutical benefits of LCAF RT in comparison with conventional fractionation for EC.^{14–16} Therefore, concurrent LCAF RT and chemotherapy have been widely accepted as a standard treatment for locally advanced ESCC in China. It was found that these patients had a median survival time of 30.8 months and 5-year OS rate of 40%, although Grade 3–4 and life-threatening toxicities were reported as 46% and 6% in the concurrent LCAF RT and chemotherapy group; hence, better survival was observed this group than in the LCAF RT alone group.¹²

Our previous studies had evaluated the dose-limiting toxicities (DLTs) and outcomes of concurrent selective lymph node (SLN) LCAF RT and capecitabine/pemetrexed plus cisplatin (CDDP).^{17,18} The results showed that the two protocols were safe and achieved encouraging outcomes. However, the toxicities were still somewhat higher. Recently, CCRT using oral fluoropyrimidine (S-1) and CDDP for the treatment of advanced EC was investigated^{19–21}, but data on the S-1 used in concurrent LCAF RT in EC are limited. To further decrease the side effects and to improve outcomes, we designed this Phase I trial of CCRT for patients with locally advanced ESCC. Our primary objectives were to define the feasibility, DLT, maximum-tolerated dose (MTD) and recommended dose (RD) of the chemotherapy to facilitate future clinical trials. The secondary objective was to get the critical preliminary data about response rates and survival.

METHODS AND MATERIALS

Eligibility criteria

Eligibility criteria included patients with ESCC confirmed by histopathology who had received CCRT and RT, from Stage IIA to IVA with bidimensionally measurable sites. They were required to be 18–70 years of age, with Karnofsky performance status ≥ 70 and weight loss $\leq 5\%$. The minimum laboratory requirements were as follows: absolute white blood cell count $\geq 4000 \text{ ml}^{-1}$ or greater, haemoglobin $\geq 10 \text{ g dl}^{-1}$ or greater, platelet count $\geq 1,00,000$ per ml, total bilirubin level $\leq 1.5 \text{ mg dl}^{-1}$, serum creatinine level ≤ 1.5 times the upper limit of normal or less and aspartate/alanine aminotransferase levels ≤ 2.5 times the upper limit of normal or less. The T stages were determined by CT or endoscopic ultrasonogram.²² The clinical tumour–node–metastasis (TNM) system staging was defined according to the American Joint Committee on Cancer staging system (v. 6.0).

Exclusion criteria

Exclusion criteria included patients with metastatic sites, imaging or bronchoscopic evidence of oesophageal perforation and some other serious underlying medical conditions which might potentially interrupt the planned treatments; for instance, severe cardiac diseases or uncontrolled diabetes, serious uncontrolled infections, central nervous system disorders or psychological disability. Patients were also excluded if they had previously received chemotherapy or RT.

Pre-treatment evaluation

Evaluation was performed before the initiation of the treatment, including history inquiry and physical examinations, such as oesophagoscopy, barium oesophagogram, bone scan by single-photon-emission CT and CT scan of the brain, neck, chest and abdomen. Complete blood counts with differential, serum chemistry tests (including electrolytes), liver function tests, coagulation panel, urinalysis and electrocardiogram were also required. Bronchoscopy was performed if clinically necessary. This study was conducted in accordance with applicable laws, regulations and guidelines good clinical practice rules. The ethical committees approved the study, which was carried out according to the Helsinki Declaration II. The institutional review committee approved the study. All patients had to sign informed consent after they understand the information of this trial.

Chemotherapy

Patients were initially enrolled in Dose Level 1. In this regimen, CDDP was given at 25 mg m^{-2} , by bolus intravenous infusion on Days 1–3 and Days 22–24; S-1 was administered in a de-escalating dosage with a decrement of 10 mg m^{-2} per day, from the Dose Level 1 of 80 mg m^{-2} , taken orally twice daily on Days 1–14 and Days 22–35, if DLTs were reached.

Radiation therapy

All patients underwent the same radiation regimen as in our previous trials,^{17,18} which was carried out by 6-MV X-ray using a two-phase irradiation schedule, (first phase: 40 Gy in 20 fractions; second phase: 19.6 Gy/1.4 Gy twice a day in 14 fractions). The gross tumour volume is composed of a primary tumour, according to an overall judgment of chest CT, oesophageal barium imaging and oesophageal endoscopy, coupled with the metastatic lymph nodes. The clinical tumour volume of the first-phase RT included the primary tumour spreading by 3 cm in the cranio-caudal direction and involved regional lymph node groups.^{23–25} According to the lymph node groups defined by Japanese guidelines,^{26,27} the neck and upper chest oesophageal SLN irradiation fields cover Group 104, Group 107 and part of Group 108. For lesions involving the middle part of the oesophagus, the radiation field should include Group 104 and Groups 106–108, as well as some part of Group 110. For lesions involving the lower oesophagus, the radiation field should cover Groups 104, 106 and 108 and 1–3, 7 and 9 lymph nodes. The planning tumour volume was generated with a 10-mm margin added to the clinical tumour volume. For the first phase of RT, conventional fractionated irradiation mode was used for 2.0 Gy per fraction to a total dose of 40 Gy. In the second phase of RT, accelerated hyperfractionated radiation was employed. Relative to the first stage, the irradiation target of selective lymph node regions was cut. All patients received LCAF RT at 1.4 Gy per fraction twice a day, 5 days per week, for 1.4 weeks, with a total dose of 19.6 Gy. Planning optimization endeavoured to meet the following treatment planning goals: $> 95\%$ of the planning tumour volume covered by the prescription isodose line, volume of bilateral lung receiving $> 20 \text{ Gy}$ of $\leq 30\%$, spinal cord maximal dose $\leq 50 \text{ Gy}$, heart V_{50} of $\leq 33\%$, V_{45} of $\leq 67\%$, liver V_{35} of $\leq 50\%$, stomach maximal dose $\leq 50 \text{ Gy}$ and small intestine maximal dose $\leq 50 \text{ Gy}$. The RT began from the first day of treatment. No modifications to the fraction size or total dose were permitted during RT.

Figure 1. Kaplan–Meier plot of overall survival.

Adverse effect assessment

Adverse effects were evaluated at least weekly during CCRT according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (v. 3.0).

Study design and end points

In the present study, the schedules for CDDP and intensity-modulated radiotherapy (IMRT) were fixed, with only S-1 being prescribed using a minus dose-escalation schedule. The initial dose of S-1 was 80 mg m^{-2} (Level 1), with doses escalated to 70 mg m^{-2} (Level 2) and 60 mg m^{-2} (Level 3). The MTD was defined as the dose level of S-1 that produced DLTs in three or more of the five patients. If MTD was observed in the initial five patients, the dose level of S-1 was decreased to the next level. If DLT occurred in less than or equal to two of the first five patients, five additional patients were treated with the same dose of S-1. On the basis of several clinical trial reports of S-1, together with other cytotoxic agents, locally advanced and metastatic EC, the maximum dose of S-1 was set at 80 mg m^{-2} twice daily.^{19–21} The dose level just below the MTD was defined as the RD for further Phase II study. As soon as the RD was determined, additional five patients were required to further evaluate the safety of RD. DLTs were defined as (1) $\geq$ Grade 3, neutropenia; (2) febrile neutropenia $>38^{\circ}\text{C}$ and absolute neutrophil count <500 per μL ; (3) $\geq$ Grade 4, thrombocytopenia; (4) any other $\geq$ Grade 3 non-haematologic toxicities, including nausea, vomiting, dermatitis, diarrhoea and oesophagitis, which did not improve within 2 days after appropriate management was commenced; and (5) treatment interruption lasting more than 1 week.

Treatment response was evaluated 6–8 weeks after the end of chemoradiotherapy by CT and barium oesophagogram according to the World Health Organization criteria.²⁸ Survival time was measured from the day of registration until the date of death; living patients were censored at the date of last follow-up. Patterns

of first failure were classified as local, regional or distant. The sites of failure were recorded as local, regional or distant. The Kaplan–Meier method was used to estimate OS.

The primary objectives of this study were to determine the MTD, RD, DLTs, safety profile of S-1 and CDDP when given concurrently with LCAF IMRT to patients with advanced ESCC. The secondary objective was to get the critical preliminary data about response rates and survival.

RESULTS

Patient characteristics

15 patients with ESCC (male/female 13/2; cervical/upper/middle/lower 4/5/5/1) were enrolled in the study from August 2011 to December 2012. The patient characteristics are summarized in Table 1. One patient had stage T2N1M0, two patients T3N0M0, six patients T3N1M0, one patient T4N0M0, four patients T4N1M0 and one patient T4N1M1a.

Table 1. Patient characteristics

Characteristics	Number
Number of patients	15
Gender (M/F)	13/2
Age range (median)	45–70 (59)
Cervical/upper/middle/lower	4/5/5/1
KPS range (median)	80–100 (90)
Dysphagia grade	
1/2/3	6/8/1
Clinical stage	
IIA/IIB/III/IVA	2/1/11/1

F, female; KPS, Karnofsky performance status; M, male.

Toxicities and recommended dose level

The adverse effects are summarized in Table 2. All patients were assessable for toxicities. In the initial five patients entered into Dose Level 1 (S-1, 80 mg m⁻²), two patients developed DLTs, which were Grade 3 neutropenia. MTD was not reached on the basis of the principle; thus, five additional patients were treated with the same dose of S-1. In these patients, one patient experienced Grade 3 neutropenia and Grade 3 dermatitis. Hence, we inferred that this dose of S-1 was safe and tolerable. To further validate our inference, we selected the last five patients, and DLTs occurred in only one patient, which was Grade 3 dermatitis. Patients with neutropenia required granulocyte colony stimulating factor treatment, and it took 3 days for them to recover completely. The dermatitis was cured by topical ointment, blowing oxygen and keeping dry. It took about 1 month for the patients to recover completely from dermatitis. Dose Level 1 (80 mg m⁻²) was regarded as the RD of S-1.

Treatment responses

The treatment responses are summarized in Table 3. The objective response rate was 100% for the primary tumours; complete response and partial response were observed in 10 and 5 patients, respectively. Regarding metastatic lymph nodes, complete response, partial response and stable disease were observed in 6, 5 and 1 patient, respectively, with the overall response rate of 91.7%.

Survival

The median follow-up time was 30 months, ranging from 8.2 to 44.3 months until the last follow-up date on April 2015.

Currently, a total of 11 patients are alive, while 3 patients died of local disease recurrence; 1 patient died of distant metastasis. Of the living patients, 1 patient experienced left armpit lymph node metastasis, abdominal lymph nodes and lung metastasis at 10.3 months and the other 10 patients had no evidence of disease relapse. The Kaplan–Meier-estimated OS rates at 1 year, 2 years and 3 years were 86.7%, 73.3% and 73.3%, respectively (Figure 1). And the progression-free survival rates at 1 year, 2 years and 3 years were 66.7%, 60% and 60%, respectively (Figure 2).

DISCUSSION

According to a series of studies implemented by the Radiation Therapy Oncology Group (RTOG),^{3–6,29} CCRT was established as a standard approach for patients with locally advanced EC. Despite of the great improvement of local control and survival, the locoregional failure and life-threatening side effects were as high as 50% and 20%, respectively,⁶ which may increase the subsequent treatment and cost and decrease the quality of life. In addition, the major patterns of failure for locally advanced EC were local control failure and metastasis. Thus, increasing the local control rate of EC and control treatment-related toxicities became the most important problems to be solved.

On account of the currently available research evidence, CDDP-based chemotherapy is a reasonable regimen. Because CDDP plays a role in radiosensitization, it has been hypothesized that patients with EC could benefit from CCRT based on CDDP. RTOG 85-01 exactly revealed that combined-modality therapy, that is current RT plus fluorouracil (5-FU) in combination with CDDP, significantly

Table 2. Adverse effects

Adverse effects	Grade (N1 = 5)				Grade (N2 = 5)				Grade (N3 = 5)			
	0	1	2	3	0	1	2	3	0	1	2	3
Haematologic												
Leukopenia	0	0	3	2	1	1	3	1	1	1	3	0
Neutropenia	0	2	1	2	2	2	0	1	2	1	2	0
Haemoglobin	1	2	2	0	2	3	0	0	2	3	0	0
Platelets	3	2	0	0	4	1	0	0	1	0	4	0
Anorexia	2	3	0	0	1	4	0	0	5	0	0	0
Mucositis	0	3	2	0	1	3	1	0	2	2	1	0
Nausea/vomiting	0	5	0	0	0	3	2	0	0	4	1	0
Non-haematologic												
Diarrhoea	4	1	0	0	5	0	0	0	5	0	0	0
Asthenia	5	0	0	0	4	1	0	0	5	0	0	0
Oesophagitis	0	4	1	0	0	3	2	0	0	3	2	0
Tracheo-oesophageal fistula	5	0	0	0	5	0	0	0	5	0	0	0
Dermatitis	0	3	2	0	0	4	0	1	0	4	0	1
Pneumonitis	4	1	0	0	5	0	0	0	5	0	0	0
Hepatotoxicity	4	1	0	0	5	0	0	0	5	0	0	0
Nephrotoxicity	5	0	0	0	5	0	0	0	5	0	0	0

Table 3. Treatment responses

Patient number	Clinical stage	Number of LN	Histology	Response of primary cancer	Response of LN
1	T3N1	2	SCC	CR	CR
2 ^a	T2N1	2	SCC	CR	PR
3	T3N1	4	SCC	CR	SD
4	T4N1	2	SCC	CR	CR
5	T3N1	3	SCC	CR	CR
6 ^b	T4N1	3	SCC	PR	PR
7 ^c	T4N1	1	SCC	PR	PR
8	T3N1	3	SCC	CR	CR
9	T3N0		SCC	PR	
10 ^d	T4N1	4	SCC	CR	CR
11 ^e	T3N1	1	SCC	CR	CR
12	T3N0		SCC	PR	
13	T3N1	1	SCC	CR	PR
14	T4N1M1a	3	SCC	CR	PR
15	T4N0		SCC	PR	

CR, complete response; LN, lymph node metastasis; PR, partial response; SCC, squamous-cell carcinoma; SD, stable disease.

^aDied of local recurrence after 12.1 months.

^bDied of local recurrence after 15.5 months.

^cDied of local recurrence after 10.3 months.

^dDied of distant metastasis after 8.2 months.

^eThe left armpit lymph node metastasis, abdominal lymph nodes and lung metastasis at 10.3 months.

improved the local control and OS compared with radiation therapy alone.⁶ RTOG 94-05 further demonstrated that 5-FU in combination with CDDP plus concurrent RT was effective for patients with locally advanced EC. However, RTOG trials and other studies also showed a high incidence of serious toxicities, such as approximately 50% acute Grade 3–4 leukocytopenia, which leads to poor compliance.^{3–5,30} Even with the presence of toxicities, dual

chemotherapy based on CDDP combined with current RT was recommended in the guidelines.²⁹ As a new biochemical modulator of 5-FU, S-1, an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine based on the biochemical modulation of 5-FU, is increasing being used in clinical practice because of its advantages in oral formulation and continuous delivery without intravenous infusion compared with 5-FU.

Figure 2. Kaplan–Meier plot of progression-free survival.

LCAF IMRT can reduce tumour-cell regeneration and shorten the overall treatment time.⁷ Furthermore, promising outcomes have been shown in concurrent LCAF IMRT and chemotherapy. However, there are still many controversial issues. A Phase 3 study enrolled 111 patients with ESCC, who were randomized to receive concurrent LCAF + chemotherapy (LCAF + CT) or LCAF alone (LCAF), during chemotherapy using CDDP 25 mg m⁻² daily and 5-FU 600 mg m⁻² daily on Days 1–3 every 4 weeks.¹² Even though there was no statistical difference, the median survival time of the LCAF + CT arm was longer than that of the LCAF arm (30.8 months vs 23.9 months; $p = 0.310$). The results showed a tendency towards better survival in patients who received combined-modality therapy. Unfortunately, combined therapy also took severe and life-threatening mortality rates; 50% patients experienced Grade 3 or worse acute toxicity, which resulted in poor compliance, with only 43% patients completing planned chemotherapy. However, the two-dimensional RT used may have contributed to the high rate of toxicities in some way.

So far, standard chemotherapy concurrent with LCAF IMRT has not yet been determined. Several factors, such as irradiation field, irradiation technology, chemotherapy regimens and so on, are likely to affect the outcome. Many modalities to combine chemotherapy with RT have been explored. We have conducted two Phase I clinical studies of concurrent LCAF RT, CDDP and capecitabine/pemetrexed for locally advanced ESCC.^{17,18} Especially, in addition to the partial patients irradiated with three-dimensional RT in earlier study and all patients experienced IMRT in the late study, SLN radiation was urged in our studies. These two protocols were safe, tolerated and achieved encouraging outcomes, while the toxicities were somewhat severe. To alleviate the adverse events and improve the outcomes of CCRT and LCAF IMRT, we conducted this Phase I trial. In the present study, we applied the same SLN LCAF IMRT regimen as in the previous study and just changed

the CCRT into CDDP and S-1.^{17,18} When the RD of the S-1 in 80 mg m⁻² was administered twice daily on Days 1–14 and Days 22–35, the DLTs that mainly occurred were Grade 3 neutropenia and dermatitis, and only 26.7% (4/15) patients in this study experienced Grade 3 toxicities. No Grade 4 or more severe toxicities occurred. The toxicities were slighter and response rates were encouraging in this trial in comparison with other previous studies.^{3–6,8,9,31–33}

Given the overall size of this study, the results of the follow-up have been reviewed cautiously. However, the high response rate, milder toxicities and OS time when administering S-1, CDDP and LCAF RT were encouraging and support further Phase II or Phase III trial testing in locally advanced ESCC.

In conclusion, therapeutic regimens concurrent with SLN LCAF IMRT, S-1 and CDDP achieved excellent response rates, milder toxicities and favourable survival rates for locally advanced ESCC. Further randomized studies could be carried out. The recommended regimen for Phase II studies is SLN LCAF IMRT plus concurrent S-1 (80 mg m⁻² twice daily on Days 1–14 and Days 22–35) and CDDP (25 mg m⁻² on Days 1–3 and Days 22–24).

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