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Phase II Trial of Intensity-Modulated Radiotherapy Concurrent With Chemotherapy for Postoperative Node-Positive Esophageal Squamous Cell Carcinoma

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The aim of this study was to evaluate the efficacy and toxicity of intensity-modulated radiotherapy concurrent with weekly docetaxel in patients with node-positive esophageal squamous cell carcinoma after radical surgery. Between January 2011 and December 2013, a total of 46 eligible patients were enrolled. All patients received intensity-modulated radiotherapy concurrent with weekly docetaxel (20 mg/m^2). Patients were treated 5 days per week at 2.0 Gy/day. The total dose of external radiotherapy given was 50 Gy in 25 fractions. The primary endpoints included treatment completion and safety. The secondary endpoint was to assess whether the approach would achieve a 1-year survival rate of 80% or higher. The median duration of follow-up was 18 months (range: 2–41 months). The 1-year overall survival and progression-free survival rate were 91.2% and 80.4%, respectively. The major acute toxicities were esophagitis and neutropenia. While most cases were grade 1 or 2, grade 3 neutropenia and esophagitis were observed in seven (15.2%) and five patients (10.9%), respectively. The toxicities were controllable and transitory. There were no unexpected cases of serious adverse events or treatment-related deaths. Our study confirms that intensity-modulated radiotherapy with concurrent weekly docetaxel is an effective and safe treatment in postoperative node-positive patients with esophageal squamous cell carcinoma. The identified treatment regimen is of interest for a phase III trial.

Key words: Esophageal cancer; Radical surgery; Intensity-modulated radiotherapy; Chemotherapy; Chemoradiotherapy (CRT)

INTRODUCTION

Although the benefit of neoadjuvant chemoradiotherapy (CRT) for esophageal cancer has been proven in not only several meta-analyses[1,2] but also a major phase III randomized trial[3], surgical resection currently remains the preferred treatment for esophageal tumors that are resectable without evidence of distant metastases. Nevertheless, the optimal management for patients who have undergone surgery has not been established, especially those with postoperative node-positive esophageal cancer[4–7].

Docetaxel has shown extensive cytotoxic activity in animal models, as well as antitumor activity against several common cancers in clinical studies[8–10]. Clinical trials of single-agent docetaxel have been reported in patients with esophageal cancer[11]. A phase I study by Mauer et al. confirmed the treatment efficacy of daily radiation concurrent with weekly docetaxel (20 mg/m^2) in 29 patients with advanced non-small cell lung or esophageal cancer[12]. Another study has shown that weekly docetaxel with concurrent radiotherapy is effective in poor prognosis esophageal cancer patients, leading to a lower incidence of severe esophagitis compared with that in cisplatin-based CRT[13].

Several studies have recently suggested the survival benefit of postoperative radiotherapy or CRT in lymph node-positive esophageal squamous cell carcinoma[14–16]. Therefore, we designed a phase II study of intensity-modulated radiotherapy with weekly docetaxel in patients with lymph node-positive esophageal squamous cell carcinoma after radical surgery. The aim of the study was to evaluate the efficacy and toxicity of this concurrent CRT regimen.

MATERIALS AND METHODS

Eligibility

Before the patients were recruited into the CRT study, all patients underwent a physical examination and a complete blood cell count with differential serum chemistry

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analysis, chest X-ray, ECG, and computed tomography scan of the neck/thoracic/abdomen and other target sites. The clinical staging of each patient was determined according to the Clinical Staging Standard for Esophageal Carcinoma Treated with Non-Surgical Methods proposed by an expert panel and published in the *Chinese Journal of Radiation Oncology* in 2010[17]. All patients fulfilled the following eligibility criteria: male and female aged 18 to 70 years; R0 (no residual microscopic disease) resection received at the original surgery (left thoracotomy approach for esophageal cancer with chest, abdomen field lymph node dissection) and histological confirmation of node-positive esophageal squamous cell carcinoma after the surgery; Karnofsky performance status not less than 70; and appropriate hematological, hepatic, and renal function (white blood cell count: $\geq 4.0\times10^9$/L, red blood cell count: $\geq 3.5\times10^{12}$/L, platelet count: $\geq 80\times10^9$/L, hemoglobin: ≥120 g/L, alanine transaminase: ≤40 U/L, serum creatinine: ≤133 μmol/L, and urea nitrogen: ≤6 mmol/L). The exclusion criteria included pregnant or lactating patients; serious complications (severe heart disease, pulmonary fibrosis, interstitial pneumonitis, and tendency for bleeding); previous treatment with radiotherapy or chemotherapy; and distant metastases or local recurrences. All patients signed the informed consent right before receiving CRT. This study was approved by the ethics committee at the Jiangsu Cancer Hospital (ChiCTR-TNC-10001140).

Treatment Plan

The CRT was started 1 month after the original surgery and was completed within 6 weeks. Patients were placed in a supine position and immobilized in a vacuum bag with hands crossed on top of their head. According to a previous study[18], the clinical target volume (CTV) included the supraclavicular areas and the superior mediastinum in patients with upper thoracic esophageal cancer; the supraclavicular areas and the superior and inferior mediastinum in patients with middle thoracic esophageal cancer; and the superior and inferior mediastinum in patients with lower thoracic esophageal cancer. The original tumor bed and the anastomosis were included in all patients. Superior mediastinal lymph node prophylactic radiotherapy was performed on all patients. The planning target volume (PTV) was generated using a uniform 0.5-cm expansion beyond the borders of the CTV. All organs at risk (e.g., heart, lung, and liver) were outlined. The total dose of external radiotherapy given was 50 Gy in 25 fractions. Patients were treated 5 days per week at 2.0 Gy/day. All radiation treatments were delivered as intensity-modulated radiotherapy within 6 weeks after surgery. Megavoltage photon energy ≥6 MV was used. Exposure of lungs, heart, spinal cord, kidney, and liver to radiation was avoided as much as possible.

Patients received a 30-min intravenous (IV) infusion of 20 mg/m^2 docetaxel every week for a maximum of 5 weeks. One hour before chemotherapy, patients received dexamethasone (10 mg, IV) to prevent a hypersensitivity reaction. Complete blood counts were performed weekly before each docetaxel infusion. When the granulocyte count was <2,000/ml and/or the platelet count was <50,000/ml, chemotherapy was delayed for 1 week or longer until the hematologic count was recovered.

Follow-Up

Toxicity assessments for all patients were performed using the criteria defined by Kluetz et al[19]. Follow-up examinations were performed every month during the first year after CRT and then every 3 months during the second year and every 6 months thereafter. The diagnosis of failure was established by CT scan, ultrasonography, and endoscopic examination with biopsies. More selective investigations such as positron emission tomography were carried out based on specific symptomatology, clinical examination, and biochemical profile. The site and date of the first relapse and the date of death were recorded.

Statistical Analysis

On the basis of a 1-year survival rate of 60% reported in the literature[4–6], it was decided that the arms would be of interest for a phase III trial if the 1-year survival rate was ≥80%. Forty-two assessable patients for the treatment were needed to test this hypothesis, which corresponded to a hazard reduction of 50%, with a one-sided type I error of 0.05% and 80% power[20]. A 10% adjustment for data attrition resulted in a sample size of 46 patients. Survival periods were calculated from the time of surgery. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. A secondary outcome was toxicity level. The study was designed to end early in the event of excessive toxicity. At any point, if the rate of patient death resulting from treatment reached 10%, then accrual would stop. For example, if death occurred in more than 2 of the first 10 patients, accrual would be terminated. All statistical tests were carried out using SPSS 9.0 for windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the Patients

Between January 2011 and December 2013, 46 patients who met the inclusion criteria received intensity-modulated radiotherapy concurrent with weekly docetaxel. None of the patients were eliminated according to the exclusion criteria. All curative surgical resection consisted of a transthoracic en bloc esophagectomy, including an abdominal and a mediastinal lymphadenectomy. Patient

characteristics are summarized in Table 1, including age, gender, tumor category, lymph node category, clinical staging, tumor location, UICC stage, tumor differentiation, tumor length, tumor size, lymphovascular invasion, and number of dissected lymph nodes.

Survival

As of December 2014, 37 patients were still alive, and 7 patients had died, including 4 who died from metastasis and 3 from recurrence. There were two patients lost to follow-up with their fates unknown to us. They were considered dead for computation of the survival curves (Fig. 1). The patterns of failure in 46 patients are shown in Table 2. Sites of first failure were as follows: celiac node in three, mediastinum node in two, cerebral in two, supraclavicular node in one, anastomosis in one, lung in one, liver in one, chest wall in one, bone in one, and more than two sites in three. The median duration of follow-up at the time of this analysis was 18 months (range: 2–41 months). The OS for 1 year was 91.2%, and the PFS for 1 year was 80.4%.

Table 1. Patient Characteristics

Characteristic	Value [*n* (%)]
Age, median (range)	57 (44–69)
Gender	
Female	8 (17.4)
Male	38 (82.6)
Tumor category	
T1	3 (6.5)
T2	12 (26.1)
T3	30 (65.2)
T4	1 (2.2)
Lymph node category	
N1	28 (60.9)
N2	15 (32.6)
N3	3 (6.5)
Clinical staging	
II	15 (33)
III	25 (54)
IV	6 (13)
Tumor location	
Upper thoracic	4 (8.7)
Mid-thoracic	24 (52.2)
Lower thoracic	18 (39.1)
UICC stage	
II	13 (28.2)
III	30 (65.2)
IV	3 (6.5)
Tumor differentiation	
Low	24 (52.2)
Middle	17 (37.0)
High	5 (10.8)
Tumor length	
<3 cm	7 (15.2)
3–6 cm	33 (71.7)
>6 cm	6 (13.1)
Tumor size	
<25 cm^3	4 (9)
25–75 cm^3	30 (65)
>75 cm^3	12 (26)
Lymphovascular invasion	
Positive	14 (30.4)
Negative	32 (69.6)
Number of dissected lymph nodes	
3–12	31 (67.4)
13–30	15 (32.6)

Adverse Events

Adverse events are summarized in Table 3. The major acute toxicities were esophagitis and neutropenia, with an incident rate of 63.0% (29/46) and 60.9% (28/46), respectively, at week 5. While most cases were grade 1 or 2, grade 3 neutropenia and esophagitis were observed in seven (15.2%) and five patients (10.9%), respectively. These episodes of grade 3 neutropenia and esophagitis were controllable and transitory, and patients were therefore able to complete the regimen without suspension of treatment or reduction of dose in the next week of chemotherapy. Grade 4 neutropenia and esophagitis were observed in none of the patients. The incidence rate of thrombocytopenia was initially low at week 1 (2/46, 4.3%) and was slightly increased at week 3 (6/46, 13.0%). Liver dysfunction occurred in five patients at week 5. Other adverse events including nausea, anorexia, diarrhea, and fatigue were observed in three, one, one, and two patients, respectively. There were no unexpected cases of serious adverse reaction or treatment-related deaths. All adverse reactions were symptomatically treated in a timely manner, and no patient withdrew from the study because of toxic events.

DISCUSSION

Despite the use of radical surgery, esophageal cancer frequently recurs in the lymph nodes at cervical, mediastinal, and abdominal regions, especially in patients who were postoperative node positive[21]. Until recently, the prognosis of patients with postoperative lymph node recurrences of esophageal cancer was disappointing. The 3-year OS rate was approximately 5%[22]. According to the principle that prophylactic therapy is superior to salvage treatment and on the basis of our former studies[18,22,23], we herein investigated intensity-modulated radiotherapy concurrent with weekly docetaxel in node-positive patients after radical surgery of esophageal squamous cell carcinoma.

Ionizing radiation causes direct and indirect DNA structural damage, especially during the G_2/M phases of cell cycle, which disrupts viable cell division, eventually

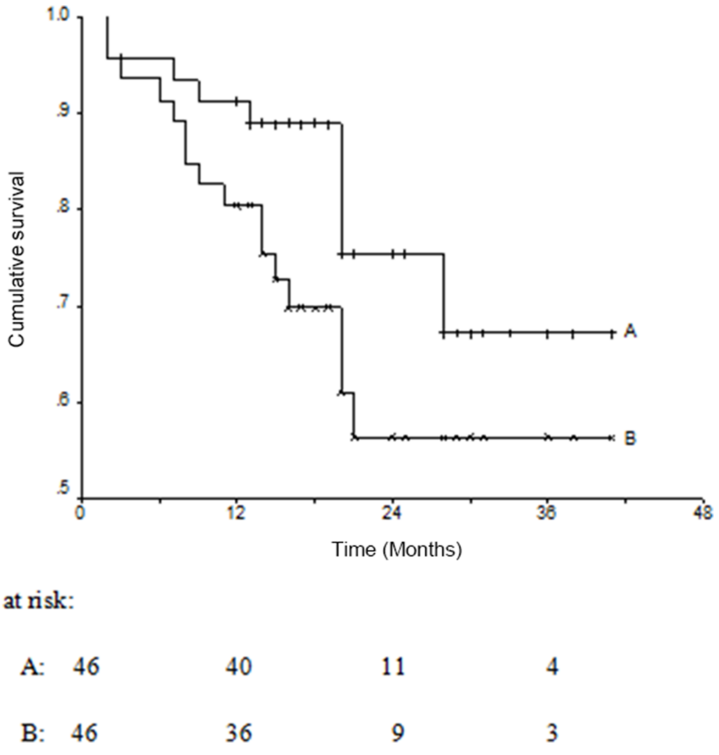

Figure 1. Kaplan–Meier curves of (A) overall and (B) disease-free survival of eligible patients.

leading to tumor cell death. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function, which results in the inhibition of mitosis and thus impairment of tumor cell division. Phases I and II clinical studies have shown that docetaxel, given either as a single agent or as part of combination therapy, is safe and efficacious for the treatment of esophageal cancer[11–13]. Our results demonstrated that intensity-modulated radiotherapy concurrent with a weekly docetaxel arm achieved the hypothesized 1-year survival rate of 80% or higher. Docetaxel can disrupt normal division during the M phase of cell cycle and thus potentially radiosensitize the cytotoxic effects of radiotherapy. The significant survival benefit in our trial might be attributed to the potential synergistic effect between radiation and docetaxel.

The extent of lymphadenectomy for esophageal squamous cell carcinoma has been well recognized as a key that influences the outcome of surgical treatment for esophageal squamous cell carcinoma[24–27]. Although the required minimal number of resected lymph node stations remains controversial, some studies have suggested a resection of 10 nodes for pT1, 20 for pT2, and ≥30 for pT3/T4[28]. Most of our patients (67.4%) had only 3–12 lymph nodes dissected, suggesting that the lymphadenectomy in these patients might be inadequate. For that reason, prophylactic CRT was performed in these patients. Certainly, it is possible that CRT compensated for the inadequate nodal dissection in these patients, leading to an underestimation of the efficacy of postoperative CRT. Therefore, future trials performed in patients with adequate lymphadenectomy should yield a more accurate evaluation of the efficacy of postoperative CRT in lymph node-positive esophageal squamous cell carcinoma.

The major acute toxicities during the intensity-modulated radiotherapy concurrent with weekly docetaxel were esophagitis and neutropenia (Table 3). Esophageal reflux commonly occurs after resection, and radio- and chemotherapy might aggravate the adverse effects, leading to a high rate of posttreatment esophagitis in our study (28/46, 60.9% at week 5). In general, adverse events in

Table 2. Site of First Recurrence

Site	No. of Patients	% of All Patients (n=46)
Distant	5	10.9
Locoregional	2	4.3
Locoregional and distant	3	6.5
Unknown	2*	4.3
Total	12	26.1

*Both patients were lost to follow-up.

Table 3. Summary of Adverse Events

	No. of Patients				
Adverse Event	Week 1	Week 2	Week 3	Week 4	Week 5
White blood cells	12	24	33	27	29
1–2 grade	12	22	33	24	27
3–4 grade	0	2	0	3	2
Red blood cells	1	1	2	2	3
1–2 grade	1	1	2	2	3
3–4 grade	0	0	0	0	0
Platelets	2	2	6	6	5
1–2 grade	2	2	6	6	5
3–4 grade	0	0	0	0	0
Hepatic	2	1	2	2	5
1–2 grade	2	1	2	2	5
3–4 grade	0	0	0	0	0
Nausea	1	0	0	2	0
1–2 grade	1	0	0	2	0
3–4 grade	0	0	0	0	0
Anorexia	0	1	0	0	0
1–2 grade	0	1	0	0	0
3–4 grade	0	0	0	0	0
Diarrhea	0	0	0	1	0
1–2 grade	0	0	0	1	0
3–4 grade	0	0	0	0	0
Fatigue	0	1	0	1	0
1–2 grade	0	1	0	1	0
3–4 grade	0	0	0	0	0
Esophagitis	2	10	19	27	28*
1–2 grade	2	10	18	25	25
3–4 grade	0	0	1	2	3

*Including one case of anastomotic leakage.

our study were as expected, including grade 1 or 2 nausea, anorexia, diarrhea, and fatigue that occurred in three, one, one, and two patients, respectively. All adverse reactions were symptomatically treated in a timely manner, and no patient withdrew from the study because of toxic events. There were no unexpected cases of serious adverse events or treatment-related deaths, which might be attributed to two reasons. First, the radiation was carefully applied in all patients to avoid exposure of important organs including lungs, heart, spinal cord, kidney, and liver. Second, both the total radiation dose (50 Gy) and weekly docetaxel dose (20 mg/m^2) were modest. Consistently, previous studies have also recommended a weekly docetaxel dose of 20 mg/m^2 with concurrent radiotherapy as a safe and efficient regimen for the treatment of esophageal cancer[12,13].

Some limitations of the present study need to be addressed. First, even though the current trial reached our primary and second endpoints, median follow-up (18 months) is too short to draw strong conclusions. Until definitive phase III data are available, such regimens should be restricted to the clinical trial settings. Moreover, adenocarcinomas and squamous cell carcinoma of the esophagus are two tumor entities with different patient characteristics, pathogenesis, and especially survival rate and therefore require different therapeutic strategies. Since all patients in our trial had squamous cell carcinoma, whether the current treatment regimen could have a similar efficacy and safety in adenocarcinoma patients needs further investigation.

In summary, our study confirms that intensity-modulated radiotherapy with concurrent weekly docetaxel is an effective and safe treatment in postoperative node-positive patients with esophageal squamous cell carcinoma. The identified treatment regimen is of interest for a phase III trial.

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