RESEARCH ARTICLE

Phase II Study of Docetaxel (Aisu®) Combined with Three-dimensional Conformal External Beam Radiotherapy in Treating Patients with Inoperable Esophageal Cancer

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Abstract

Objective: This study was designed to investigate treatment efficacy and side effects of concomitant Aisu® (docetaxel) with three-dimensional conformal external beam radiotherapy for the treatment of inoperable patients with esophageal cancer. Methods: Inoperable patients were treated with three-dimensional conformal external beam radiotherapy (5/week, 2 GY/day, and total dose 60GY) plus docetaxel (30-45 mg/m^2, iv, d1, 8). Results: Twenty eight patients met the study eligibility criteria and the response rate was evaluated according to RICIST guidelines. Among 28 patients, 2 achieved CR, 22 PR, 3 SD and 1 patient was documented PD. Mild gastrointestinal reaction and bone marrow suppression were also documented. All treatment related side effects were tolerable. Conclusion: Three-dimensional conformal external beam radiotherapy combined with docetaxel is an active and safe regimen for inoperable patients with esophageal cancer.

Keywords: Conformal radiotherapy - docetaxel - inoperable esophageal cancer

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Introduction

According to 2002 statistical estimation, age-standardized mortality of esophageal cancer (EC) in China was 21.6/10^5 for males and 9.6/10^5 for females, in contrast to 9.6/10^5 and 3.9/10^5 worldwide, 5.1/10^5 and 1.2/10^5 in the United States, 7.5/10^5 and 1.1/10^5 in Japan, for males and females, respectively (Song et al., 2012). Even within China, a big geographic variation is observed where a higher incidence is documented in Henan, northern Jiangsu, and Shanxi province (Song et al., 2012). SiYang hospital is located in northern part of Jiangsu province and is within this high risk area. EC is usually diagnosed at advanced stage in this area with combined chemo- and/or radio-therapy remaining a main treatment modality (Gu M., et al, 2013). A lot of EC patients in SiYang area are diagnosed in advanced and un-resectable stage because of poor healthy consciousness of the local people. Only 10%-15% patients were reported to have long-term survival after surgery or radiotherapy (Nishimaki et al., 2004). Usually, concurrent radio- and chemotherapy is considered a standard treatment for inoperable patients in this setting (Nishimaki et al., 2004). However, it is not known what combination is the best option. We focused on inoperative EC patients to observe if docetaxel combined with three-dimensional conformal external beam radiotherapy is a proper choice.

Materials and Methods

Eligibility criteria

All patients involved in this study were required to be histologically confirmed with EC, aged 18-75 years, to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and a life expectancy of ≥3 months. Patients were staged III or IV and not indicated for surgery. The patients had no other contraindication. The exclusion criteria included the following: pregnant or nursing women; hemoglobin≤100g/L, leucocyte≤3.6×10^9/L, platelets count≤10×10^{11}/L, and hepatic or renal function abnormal, as well as no clearly evaluating lesions.

Methods

Before treatment, all measurable lesions were documented by chest, upper abdominal computed tomography (CT) scan, bone scanning or other necessary examination. Three-dimensional conformal treatment was recommended when radiotherapy was conducted as the following: (1) We take GTV as the primary lesions which referenced the length from esophagography, esophagoscopy and/or intracavity ultrasound. While CTV included GTV and lymphatic drainage area, which extended 0.8 cm on the left and right based on GTV and extroverted 3 to 5 cm on upper and lower. PTV: 0.5cm extroverted on the basis of the CTV. (2) Radiation dosage

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Table 1. Main Adverse Reactions of Concurrent Radio- and Chemotherapy

	0	I	II	III	IV	Incidence(%)
Bone marrow suppression	17	8	3	0	0	39.2
Gastrointestinal reactions	7	5	13	3	0	75
Radio- esophagitis	9	3	6	10	0	67.9
Liver damage	26	1	1	0	0	7.1

of 95% PTV were 2 Gy per dose and 5 doses per week and a total of 60 Gy. (3) All patients were intravenously administered 30-45 mg/m^2 Aisu® (docetaxel injection, produced by Lianyungang HengRui pharmaceutical Company) once a week for 2 consecutive weeks, and premedication was ordered routinely. All patients received full blood count, hepatic and renal functions and ECG to evaluate the safety and adverse effect before and after each cycle of chemotherapy. After two cycles of treatment, a CT scan and examination of barium meal in digestive tract, when necessary, gastroscopy is performed, to evaluate the response to treatment and the tolerability of concurrent radio- chemotherapy.

Treatment assessment

All patients should be followed up till disease progression, which was conformed by imaging technology, and document time to progression. Evaluation of response was carried out according to RECIST criteria, including complete response (CR), partial response (PR), stable (SD) and progress (PD), overall response rate (RR)= CR + PR. Adverse reaction was evaluated according to WHO and RTOG Criteria.

Research Experience

We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

Patient Characteristics

From Jan 2010 to Aug 2012, 28 eligible patients were recruited. Among 28 patients, 18 patients accepted initial treatment whereas 10 cases recurrenced after operation or post-chemoradiation; 27 patients were squamous carcinoma and 1 adenocarcinoma; 16 were male and 12 female. Age of patients ranged from 54 to 80 with a mean age of 69.1. There were 18 patients with stage III and 10 with stage IV according to TNM staging system for esophageal cancer.

Response

All 28 patients were evaluated. Among 28 cases, there were 2 CR, 22 PR, 3 SD, and 1 PD. The response rate was 85.7% (24/28).

Toxicities

Toxicities (WHO toxicity Grade) for gastrointestinal reactions, radiotherapy related esophagitis, bone marrow suppression and liver damage occurred in most of the patients. Toxicities (Table 1) were alleviated after treatment.

Discussion

China is an area with high incidence of EC (Song et al., 2012). In China, approximately 90% patients were pathologically diagnosed as squamous cell EC, which is sensitive to radiation. Thus, about 80% of patients are considered to be treated by radiotherapy to relieve symptoms and prolong survival time. However, the survival and local control rates of EC are disappointing if only single modality are considered , thus led to a need to develop more effective nonsurgical management that is definitive chemoradiotherapy (Tsuya et al., 1968). It is suggested that chemoradiotherapy was significantly superior to radiotherapy alone (Wong et al., 2003). Concurrent chemoradiotherapy reduced the mortality of 9% and 8% in patients with stageIa and IIa respectively, and improved local control rate (Wong et al., 2003).

Chemotherapeutants incorporated into chemoradiotherapy include 5-fluorouracil (5-FU), cisplatin, and mitomycin C (MMC), and taxane-based regimens were investigated as a less toxic alternative to 5-FU-based regimens. The taxanes had been identified as potential radiosensitizers when preclinical data revealed their lethal effects of inhibiting mitosis, interfering with the cell cycle, and encouraging apoptosis (Dorr et al., 1997; Kearns et al., 1997; Herscher et al., 1999; Parness et al., 1981; Manfredi et al., 1982). Taxane was shown to have significant activity in patients with metastatic esophageal cancer in the early 1990s (Ajani et al., 1994). Multiple phase II studies have evaluated taxane-based chemoradiotherapy regimens in esophageal cancer. These studies and other retrospective analyses support the conclusion that taxane-based regimens result in complete response rates and survival comparable to those attained using 5-FU-based regimens (Hainsworth et al., 1997; Kelsey et al., 2007; Kim et al., 2007). In addition, data show that rates of grade 4 esophagitis in these regimens are 5% or less (Safran et al., 2001; Brenner et al., 2004; Safran et al., 2007). Conventional radiotherapy does not concentrate adequate dose on the tumor, thus is associated with increased toxicities, especially when combined with chemotherapy. On the other hand, three-dimensional conformal external beam radiotherapy makes the dose distribution of target more reasonably and reduces radiation associated toxicities.

Inoperable patients with EC in our study were treated with three-dimensional conformal external beam radiotherapy concurrent with docetaxel. The local control rate was 85.7%. Side effects including gastrointestinal, esophagitis, bone marrow suppression and liver damage were tolerable.

In summary, the regimen of three-dimensional conformal external beam radiotherapy concurrent

with docetaxel is safe with a high local control rate for inoperable esophageal cancer patients, thus needs randomized clinical studies to further confirm its usefullness.

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