RESEARCH ARTICLE

Clinical Study on Lobaplatin Combined with 5-Fu and Concurrent Radiotherapy in Treating Patients with Inoperable Esophageal Cancer

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Abstract

Objective: To investigate short- and long-term treatment effects and side reactions of lobaplatin plus 5-Fu combined and concurrent radiotherapy in treating patients with inoperable middle-advanced stage esophageal cancer. Methods: Sixty patients with middle-advanced stage esophageal squamous cell cancer were retrospectively analyzed. All patients were administered lobaplatin (50 mg intravenously) for 2 h on day 1, and 5-Fu (500 mg/m^2) injected intravenously from day 1 to 5 for 1 cycle, in an interval of 21 days for totally 4 cycles. At the same time, late-course accelerated hyperfractionated three-dimensional conformal radiotherapy was performed. Patients were firstly treated with conventional fractionated irradiation (1.8 Gy/d, 5 times/week, a total of 23 treatments, and DT41.4 Gy), and then treated with accelerated hyperfractionated irradiation (1.5 Gy, 2 times/d, a total of 27 Gy in 9 days, an entire course of 6-7 weeks, and DT 68.4Gy). Results: All patients completed treatment, including 10 complete response (CR), 41 partial response (PR), 7 stable disease (SD), and 2 progressive disease (PD). The total effective rate was 85.0% (51/60). Thirty-nine patients had an increased KPS score. One-, 2-, and 3-year survival rates were 85.3%, 57.5%, and 41.7%, respectively. The median survival time was 27 months. The adverse reactions included myelosuppression, which was mainly degreeI and II. The occurrence rate of radiation esophagitis was 17.5%. No significant hepatic or renal toxicity was observed. Conclusion: Lobaplatin plus 5-Fu combined with concurrent radiotherapy is safe and effective in treating patients with middle-advanced stage esophageal cancer. However, this result warrants further evaluation by randomized clinical studies.

Keywords: Lobaplatin - 5-Fu; concurrent radiochemotherapy - esophageal cancer

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Introduction

In China, esophageal cancer is a malignant tumor with a high incidence. Esophageal cancer has non-specific symptoms and is difficult to detect in an early stage. More often, esophageal cancer is diagnosed in the middle-advanced stage at which time symptoms occur, and thus most patients are inoperable. At present, the use of concurrent chemoradiotherapy in the treatment of patients with inoperable middle-advanced stage esophageal cancers is the standard treatment and can significantly improve the survival rate, but the treatment-associated toxicity is significantly increased (Urba et al., 2003; Polee et al., 2003; Zhao et al., 2005). Therefore, how to choose effective chemotherapeutics with low toxicity, improve the efficacy, and reduce adverse reactions in patients is essential. Lobaplatin (LBP) is a third-generation platinum anti-cancer drug developed by the German company, ASTA. LBP is a platinum agent with the highest efficiency for single drug treatment of esophageal cancer (Schmoll, 1995; Chinese Society of Esophagenal Cancer, Chinese Anti-Cancer Association, 2011), and some clinical studies have confirmed that LBP is safe and effective in the treatment of esophageal cancer (Xingya et al., 2007; Yu et al., 2012). We retrospectively analyzed the data of 60 patients with middle-advanced stage esophageal squamous cell cancer who received LBP plus 5-Fu combined with concurrent radiotherapy, which we report as follows.

Materials and Methods

General data

The inclusion criteria were as follows: 1) during initial treatment, the pathologic evaluation confirmed the diagnosis of esophageal squamous cell carcinoma, and there were objective and measurable lesions; 2) age ≤75 years and Karnofsky score > 70 points; 3) there was no surgical indication and no contraindication for chemoradiotherapy, and the patients underwent treatment for the first time; 4) blood, liver, and kidney functions were normal, and there was no apparent abnormality in cardiopulmonary function; 5) there were no esophageal

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fistulas; and 6) informed consent were obtained. Sixty patients who met the requirements were enrolled into the group between January 2011 and May 2013; there were 37 males and 23 females. The patients aged in range between 45 and 75 years, with a median age of 65 years. Segmentation was assigned according to the 2002 edition of the Union for International Cancer Control (UICC) segmentation criteria (AJCC, 2002), as follows: 6 cases in the cervical segment; 19 cases in the upper thoracic segment; 32 cases in the middle thoracic segment; and 3 cases in the lower thoracic segment. Thirty-six patients were stage III and 24 patients were stage IV.

Treatment method

All patients were administered LBP (50 mg intravenously for 2 h on the 1st day), and were injected with 5-Fu (500 mg/m^2 intravenously from the 1st-5th days every 21 days for 4 cycles). At the same time, late course accelerated hyperfractionated three-dimensional conformal radiotherapy was performed as follows: the patients were first treated with conventional fractionated irradiation (1.8 Gy/d, 5 times/week, a total of 23 times, and DT41.4 Gy; then the patients were treated with accelerated hyperfractionated irradiation (1.5 Gy, 2 times/day, a total of 27 Gy in 9 days, an entire course of 6-7 weeks, and DT 68.4Gy).

Observational indexes

According to WHO Response Evaluation Criteria in Solid Tumors (Sun et al., 2003), the recent curative effect evaluation standard was divided into complete remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD); the effective rate was CR + PR. According to the American Cancer Institute, anticancer drug acute and sub-acute toxic reaction grade standards, the toxic reactions were divided into 0-4 grades (Sun et al., 2003). All patients were followed until the radiographic data confirmed disease progression.

Follow up

All patients were followed by means of outpatient re-examination, telephone follow-up, and follow-up letters between 10 December 2011 and 31 December 2014. The 1-, 2-, and 3-year survival rates and the number of the survived cases were calculated.

Results

Treatment results

All patients completed treatment, including 10 patients with CR, 41 with PR, 7 with SD, and 2 with PD. The total effective rate was 85.0% (51/60). Thirty-nine patients had increased KPS scores, with an average increase of 10 points.

By the end of the follow-up period, 35 patients had died and 25 patients had survived; the median survival time was 27 months. One-, 2-, and 3-year survival rates were 85.3%, 57.5%, and 41.7%, respectively. Some patients with good efficacy and patients with SD had improved subjective symptoms, and the body weights were increased slightly compared with pre-chemotherapy.

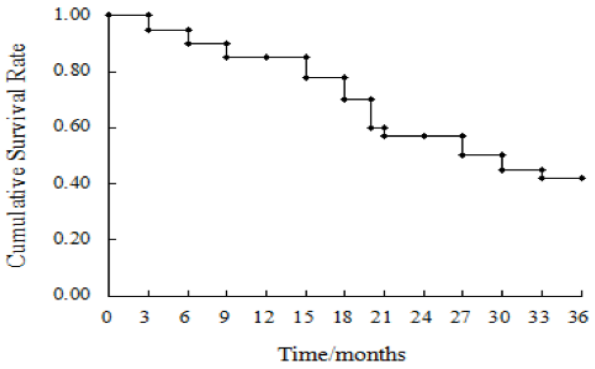

Figure 1. Survival Curve of the Patient

Adverse reactions

Routine blood testing was carried out 0.5, 1, 3, and 6 months after treatment. The number of leukocytes was decreased (degreeI-II, 45.3%; and degree III , 10.1%). The hemoglobin level was decreased (degreeI-II, 15.7%; and degree III, 5%). Blood platelet count was decreased (degree I-II, 20.1%; and degree III-IV, 5.4%). Gastrointestinal reactions including vomiting (25.8%), stomatitis (15.2%), and radiation esophagitis and mucosal ulcers (17.5%). No obvious liver and kidney toxicity, neurotoxicity, and alopecia were reported.

Discussion

It has been reported (Hongxun, 2002; Jiazhuan, 2002) that radiotherapy is the main treatment option for inoperable middle-advanced stage esophageal cancer, but the curative effect of radiotherapy alone is poor. The leading causes of death include uncontrolled local disease, recurrence, and distant metastases (Brenner et al., 2004). Combined chemoradiotherapy can produce an additive or synergistic effect, and the treatment effect of chemotherapy on distant metastasis can compensate for the limitations of the radiotherapy. The randomized clinical trial, RTOG-8501 (Herskovic et al., 1992), promoted the use of the concurrent chemoradiotherapy in the treatment of esophageal cancer. The curative effect of cisplatin plus 5-Fu combined with radiotherapy in the treatment of the middle-advanced stage esophageal cancer is definite and stable, but the toxic reaction of cisplatin is greater and some patients have a poor quality of life after its use. LBP is a third generation platinum anticancer drug developed by the German company, ASTA. LBP has been reported in the international literature to have equivalent or better effects than cisplatin and carboplatin, no renal toxicity, and no need for hydration; the gastrointestinal reactions are also mild (Mckeage, 2001).

The results of the current study showed that the total effective rate of LBP plus 5-Fu combined with concurrent radiotherapy in the treatment of patients with inoperable middle-advanced stage esophageal cancer was 85.0% (51/60), and the median remission duration was 18.5 months. The 1-, 2-, and 3-year survival rates were 85.3%, 57.5%, and 41.7%, respectively. The main adverse reactions included the following: (1) myelosuppression (all white blood cells, platelets, and hemoglobin were decreased, but which were mainly demonstrated as degreeI

and II, and the duration was short; the occurrence rate of platelet decline was 25.6%, and the occurrence rate of degree III was 5.4%; and(2)gastrointestinal reactions (the occurrence rate of degreeI and II vomiting was 25.8%; the occurrence rate of stomatitis was 15.2%, and all were reactions of degreeI and II). When this group of patients were treated, it was not necessary to give hydration or diuretic measures, no significant toxic and adverse effects, such as hepatic and renal toxicity, neurotoxicity, ototoxicity, and allergic reaction were observed. In addition to mild fatigue and hair loss, no other obvious adverse reactions were observed.

In summary, LBP plus 5-Fu combined with concurrent radiotherapy in the treatment of esophageal cancer has obvious advantages in controlling the local lesions, eliminating the potential metastatic lesions, and prolonging the survival time, which has a significant curative effect, milder adverse reactions, and better tolerance, thus providing a new choice for patients with middle-advanced esophageal cancer. The late course accelerated hyperfractionated three-dimensional conformal radiotherapy can be used as one of the preferred treatment methods for middle-advanced esophageal cancer, so as to improve the local control and survival rates, and short-term radiation reaction and long-term radiation injury can be tolerated. The chemotherapy regimen is more reasonably optimized, and is expected to be able to achieve a better curative effect because LBP has appeared on the market only for a short time. Further collection of cases are needed and long-term clinical observations should be carried out to determine the optimal doses of radiotherapy and chemotherapy drugs and the best combined chemoradiotherapy program.

References

American Joint Committee on Cancer. AJCC Cancer Staging Hand book. 6th ed. Philadelphia: Lippincott-Raven, 2002.

Brenner B, Ilson DH, Minsky BD (2004). Treatment of localized esophageal cancer. *Semin Oncol,* **31**, 554-65.

Chinese Society of Esophagenal Cancer, Chinese Anti-Cancer Association (2011). Clinical Practice Guidelines for the Diagnosis and Treatment of Esophageal Cancer [M] Beijing: China Union Medical University Press, 116-9.

Li X, Zhou F, Ren Z, et al (2007). Phase II trail of Lobaplatin, leucovorin and fluorouracil in patient s with advanced carcinoma of the esophagus. *Chin J Cancer Prev Treat*, **14**, 65-7.

Lin Y, Chen J, Li J, et al (2012). Recent results of concurrent chemoradiotherapy with lobaplatin and paclitaxel in advanced esophageal carcinoma. *Cancer Res Clinic,* **24**, 105-7.

Mckeage MJ (2001). Lobaplatin: a new antitumour platinum drug. *Expert Opin Investig Drug*s, **10**, 119-28.

Mei, J, Liu J, Yao W (2002). Concurrent chemoradiotherapy for locoregional esophageal cancer. *Chin J Clin Oncol Rehab*, **9**, 98-9.

Polee MB, Tilanus HW, Eskens FA (2003). Phase IIstudy of neo-adjuvant chemotherapy with paclitaxel and cisplatin given every 2 weeks for patients with a resectable squamous cell carcinoma of the esophagus. *Ann Onco*l, **14**, 1253-7.

Schmoll HJ, Kohne CH, Papagerorion E, et al (1995). Single angent lobaplatin is active in patients with esophageal squamous cell carcinoma: a phase II evaluation. *Proc Am Soc Clin Oncol*, **14**, 483.

Sun Y, Zhou J (2003). Manual of Medical Oncology [M] 4th edition. Beijing: People's Medical Publishing House, 2003: 106-107, 274-276.

Urba SG, Orringer MB, Ianettonni M, et al (2003). Concurrent cisplatin, paclitaxel, and radiotherapy as preoperative treatment for patients with locoregional esophageal carcinoma. *Cancer*, **98**, 2177-83.

Ye H (2002). Combined chemoradiotherapy in the in the treatment of middle-advanced stage esophageal cancers. *Cancer Res Clinic*, **14**, 187-8.

Zhao KI, Shi XH, Jiang GL, et al (2005). Late course accelerated hyperfractionated radiotherapy plus concurrent chemotherapy for squamous cell carcinoma of the esophagus: a phase III randomized study. *Int J Radiat Oncol Biol Phys*, **62**, 1014-20.