RESEARCH ARTICLE

Phase II Study on Dose Escalating Schedule of Paclitaxel Concurrent with Radiotherapy in Treating Patients with Locally Advanced Non-small Cell Lung Cancer

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Abstract

Objective: To evaluate clinical efficacy of a dose escalating schedule of paclitaxel concurrent with radiotherapy in treating patients with locally advanced non-small cell lung (NSCLC). Methods: Patients with locally advanced NSCLC were treated with conventional fractionated radiotherapy or three dimensional conformal radiotherapy (3 DCRT), concurrently with a dose escalating schedule of paclitaxel. All patients were divided into three groups, A with paclitaxel 30 mg/m^2, B with paclitaxel 60 mg/m^2 and C with paclitaxel 90 mg/m^2. Paclitaxel was repeated every week for a total of 4 or 6 weeks. Results: Among 109 patients, response rates were 68.8%, 71.1% and 71.8% (p>0.05) for group A (n=32), B (n=38), and C (n=39) respectively. Accordingly, disease control rates were 81.3%, 81.6% and 82.1% (p>0.05). Progression-free survival time was 8.0±5.0 months, 11.6±6.1 months, and 14.8±7.9 months (p<0.05), respectively. Overall survival time was 15.4±7.6 months, 18.2±8.0 months, and 22.0±7.6 months (p<0.05), one-year survival rates were 62.5%, 73.1% and 90.0% (p>0.05) and two-year survival rates were 31.3%, 38.5% and 50.0% (p<0.05) . Main side-effects were bone marrow suppression, radiation related esophagitis and gastrointestinal reaction. Conclusion: In treating patients with NSCLC, concurrent chemoradiotherapy with paclitaxel improves early response compared with conventional fractionated radiotherapy or 3 DCRT. The survival rate was improved with the addition of paclitaxel, but there was an increase in adverse reactions when the dose of paclitaxel was increased.

Keywords: Non-small cell lung cancer - concurrent chemoradiotherapy - paclitaxel - prognosis

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Introduction

Lung cancer is one of the most common malignant tumor around the world, non-small cell lung cancer (NSCLC) accounting for 75% ~ 80% (Al-Hashimi et al., 2014; Lu et al., 2013; Demirci et al., 2013). In addition, 45% of the patients who has NSCLC are usually clinical diagnosed in locally advanced (Jemal et al., 2010). Chemoradiotherapy is a major treatment for locally advanced NSCLC. Concurrent chemoradiotherapy is superior to sequential and simple chemoradiotherapy. Paclitaxel (PTX) is one of the effective agents for NSCLC. Studies show that concurrent chemoradiotherapy therapy of NSCLC, compared with pure radiotherapy and chemotherapy, has advantages in local control, recent efficient and long-term survival. However, there is an increase in adverse reaction and a decrease in patient tolerability when the dose of PTX is increased (Jemal et al., 2002; Wang et al., 2006; Chen et al., 2012). To evaluate the associations between clinical efficacy of dose escalating schedule of PTX for chemoradiotherapy in treating patients with advanced NSCLC, this study was initiated from 2010.

Materials and Methods

General Information

From January 2010 to October 2011, there were 109 inpatients (62 male, 47 female) pathologically or cytologically diagnosed with NSCLC were recruited. Age of patients ranged from 36 to 75 years of age, with median age of 65. Kanofsky score was more than 70.All patients were divided into three groups that is group A, B, and C. According to UICC TNM staging criteria in 2002, 72 patients were staged III A and 37 III B, and 69 for squamous cell carcinoma, 38 for adenocarcinoma, 2 for gland scale cancer. All patients have not been treated by radiotherapy or chemotherapy.

Methods

Radiation therapy adopts conventional segmentation or three-dimensional conformal radiotherapy. For

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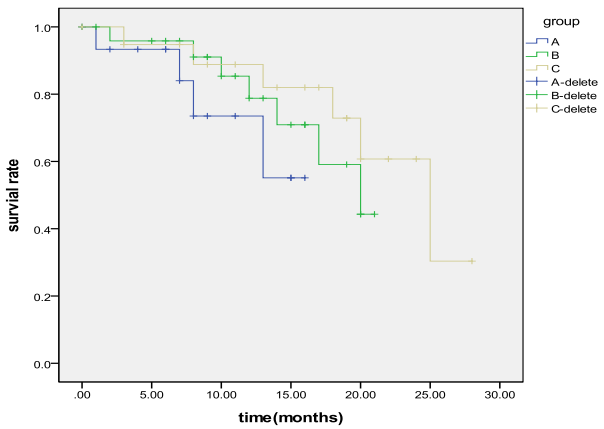

Figure 1. Progression-free Survivals

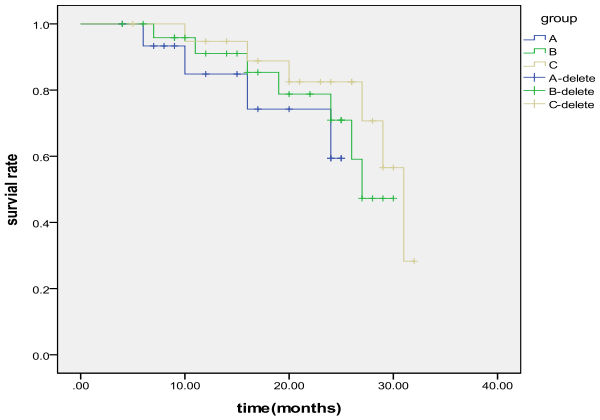

Figure 2. Overall Survivals

conventional segmentation irradiation, radiation includes primary lesion, ipsilateral lung door, mediastinum, and involvement of lymph nodes, with the total DT 60 ~ 68 Gy, using 6 ~ 15 MV X-ray (DT 1.8~2Gy/times, 5 times per week, 6 ~ 6.5 weeks for completement). For three-dimensional conformal radiotherapy, radiation is positioned by CT. Patients are supine and marked on their surface. Body model should be fixed and marked on it. CT scan (5mm) and data are transmitted to the TPS workstation. According to the international commission on radiation and measurements (ICRU) No.50 file, two clinicians should outline the tumor volume (GTV) and important viscera around. GTV expand 1.5 ~ 2.0 cm outward, forming planning target volume (PTV). After TPS, data are evaluated by dose volume histogram. Linear accelerator is 6 ~ 15 MV X-ray, also including primary lesion, ipsilateral lung door, mediastinum, and involvement of lymph nodes. Irradiation respectively sets 5 ~ 6 coplanar or not coplanar. DT is 1.8 ~ 2.0 Gy/times (five times per week). The total dose is 60 ~ 70 Gy. Before the first time for radiotherapy, accuracy of the beam position on board should be verified.

Chemotherapy: PTX is given on the first day of radiotherapy. Patients accept radiotherapy after 3h, 1 times a week on the same dosage, a total of 4 ~ 6 times. Before using PTX, routine premedication should be administrated and antiemetic should be ordered. Dose of PTX was divided into three groups, group A with 30 mg/m^2, B with 60 mg/m^2 and C with 90 mg/m^2.

After concurrent chemoradiotherapy, PTX + DDP project should be adopted for 4 cycles.

Follow-up

All patients are followed by clinic check or telephone interview. None of patients lost follow-up.

Evaluation of response

Statistical analysis on tumor size and toxicity reaction of treatment is performed on three groups respectively. Time of disease progression (PFS) and overall survival (OS) are estimated. Recent curative effect is evaluated by RECIST 1.0 standard, including complete remission (CR), partial response (PR), stable (SD), development (PD), response rate {RR= (CR + PR)/ (CR + PR+ SD+ PD)}, and disease control rates { DCR = (CR + PR+ SD)/ (CR + PR+ SD+ PD)} (Andoh et al., 2013). Chemotherapy related toxicity is documented according to NCI CTC standard, classified into 0 ~ 4 levels (Trotti et al., 2000). Radiation related toxicity is evaluated by RTOG standard (Byhardt et al., 1998). Overall survival time is calculated from the date of diagnosis to date of patients death.

Statistical analysis

SPSS 19.0 software is used for data analysis. Measurement data are shown with the from of mean ±standard deviation. T test is used to compare average. Count data are compared by chi-square test. Kaplan - Meier method is used for survival analysis. Statistically significance is defined when $p<0.05$.

Results

All 109 patients completed treatment schedule, including 32 in group A, 38 in group B, and 39 in group C.

short-term curative effect

For patients in Group A: no CR, 22 patients achieved PR, 4 patients were SD, and PD was observed in 6 patients, thus RR was 68.8%, and DCR 81.3%; for patients in Group B: 1 reported CR, 26 PR, 4 SD, 7 PD, thus, RR was 73.1%, DCR was 81.6%; in Group C: 0 CR, 28 PR, 4 SD, 7 PD, therefore, RR 71.8%, DCR 82.1%. No difference was observed among three groups ($p>0.05$).

Side effects

Treatment related main side effects are gastrointestinal reaction, bone marrow suppression, radioactive esophagitis and radioactive lung injury. Gastrointestinal reaction was mainly in I~II level; Gastrointestinal reaction in III~IV level was 4 for Group A (12.5%), 6 for Group B (15.8%), and 6 for Group C (15.4%) ($p>0.05$). Bone marrow suppression inI~II level was 10 for Group A (31.3%), 15 for Group B (39.5%), and 20 for Group C (51.3%) ($p>0.05$); Bone marrow suppression in III~IV level was 4 for Group A (12.5%), 16 for Group B (42.1%), and 20 for Group C (51.3%) ($p<0.05$). Radioactive esophagitis inI~II level was 14 for Group A (43.8%), 19 for Group B (50.0%), and 23 for Group C (59.0%) ($p>0.05$); Radioactive esophagitis in III~IV level was 2 for Group A (6.3%), 6 for Group B (15.8%), and 18 for Group C (46.2%) ($p<0.05$). Radioactive lung injury inI~II level was

4 for Group A (12.5%), 9 for Group B (23.7%), and 10 for Group C (25.6%) (p>0.05); Radioactive lung injury in III~IV level was 2 for Group A (6.3%), 4 for Group B (10.5%), and 14 for Group C (35.9%) (p<0.05).

survival analysis

PFS: Group A, B, C were 8.0±5.0 (95%CI 5.3-10.7), 11.6±6.1 (95%CI 9.1-14.0), 14.8±7.9 (95%CI 11.1-18.5) respectively, with statistically significant difference (χ^2=4.913, p=0.011).

OS: Group A, B, C were 15.4±7.6 (95%CI 11.4-19.4), 18.2±8.0 (95%CI 14.9-21.4), 22.0±7.6 (95%CI 18.4-25.6) respectively, with significant difference statistically (χ^2=3.943, p=0.042).

One year survival rate: Group A, B, C were 62.5%, 73.1%, 90.0% respectively. There was no statistically significant difference among three groups (χ^2=1.216, p=0.306). Two year survival rate: Group A, B, C were 31.3%, 38.5%, 50.0% respectively, with statistically significant difference (χ^2=5.686, p=0.010). All these results were shown in the Figure 1and Figure 2.

Discussion

The incidence of NSCLC increases in recent years (Field et al., 2013). For locally advanced NSCLC, clinical studies have shown that combined treatment is better than radiotherapy or chemotherapy, and concurrent chemoradiotherapy is superior to sequential chemoradiotherapy (Liu et al., 2013; Zhou et al., 2009). Curran et al found that median survival period of concurrent chemoradiotherapy was 15.6 ~ 17.1 months. Overall survival rates for 2 and 3 years were 22.3% and 16.9% respectively, superior to sequential chemoradiotherapy (Curran et al., 2011). Fournel et al also found that survival period of concurrent chemoradiotherapy (16.3 for median survival period) was superior to sequential chemoradiotherapy (14.5 for median survival period). Survival rates of concurrent chemoradiotherapy for 2 and 3 years were 39% and 25% respectively (Fournel et al., 2005). Therefore, concurrent chemoradiotherapy has become the standard treatment for advanced lung cancer (Wu et al., 2002; Lu et al., 2004).

Concurrent chemoradiotherapy is considered to have following advantages compared with sequential chemoradiotherapy. First, chemotherapy agents could increase sensitivity of tumor cells, especially cells lack of oxygen. Radiation could add cytotoxic effects on chemotherapeutic agents, enhancing cytotoxic effect on tumor cells. And, chemotherapy could avoid transfer of subclinical lesions, reducing the risk of distant metastases.

Chemotherapeutic agents of concurrent chemoradiotherapy for NSCLC are controversial (Yin et al., 2013). Paclitaxel, docetaxel, vinorelbine, cisplatin, carboplatin, nedaplatin, etc are considered more commonly used (Vokes et al., 2002; Ourari et al., 2012; Cufer et al., 2013; Salama et al., 2013; Sculier, 2013). Paclitaxel, as a kind of cell cycle specific broad-spectrum antitumor drug, could accumulate cells in G2, M phase of the cell cycle through microtubules resistant. Paclitaxel could also inhibit expression of Bcl-2h and Bcl-xl gene, leading to cell apoptosis, and promote oxygenation of cells lack of oxygen, as well as inhibit tumor cell proliferation. Thus, paclitaxel has obvious cytotoxic effect and radiosensitization (Chen et al., 2001; Jiang et al., 2012). Solomon et al reported that median survival rate for paclitaxel combined with radiotherapy in treatment of locally advanced NSCLC was 23.6 months. One year survival rate was 72% and two years survival rate was 49%, both higher than radiotherapy alone (Solomon et al., 2003).

However, no standard dose of paclitaxel is established for synchronous radiation at present. Our study showed that recent short-term effect in 3 doses of PTX were 68.8%, 71.1% and 71.8% respectively, with no statistical significance, suggesting that the dose of PTX with concurrent chemoradiotherapy had little influence on short-term curative effect. But, during follow-up, we found that PFS of three groups were 8.0, 11.6, 14.8 months (p < 0.05) and OS were 15.4, 18.2, 14.9 months (p < 0.05). While one year survival rate was not statistically different, two years survival rate were 31.3%, 38.5%, 50.0%, with statistical significance. These results suggest that long-term survival time was elongated with the increase of PTX dosage.

Many studies reported that short-term curative effect of concurrent chemoradiotherapy in treatment of locally advanced NSCLC was improved. However, side effects of treatment were also increased (Lu et al., 2004; Zhou et al., 2009). Clinical studies suggested that short-term side effects were serious with the increased dose of PTX. Main side effects were III ~ IV level of pain caused by radioactive esophageal injury, hematological toxicity and gastrointestinal reactions (nausea, vomiting, et al).

In conclusion, we found that short-term curative effect was improved by the use of PTX in concurrent chemoradiotherapy treatment of locally advanced NSCLC. With the increased dose of PTX, long-term survival rate was increased, while short-term side effects were also increased. Therefore, appropriate PTX dose is worth further investigated by clinical trials.

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