ADJUVANT CHEMOTHERAPY FOLLOWING RADICAL SURGERY FOR NON-SMALL CELL LUNG CANCER:A RANDOMIZED STUDY

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Abstract

Objective: To evaluate the efficacy of adjuvant chemotherapy after radical surgery for non-small cell lung cancer (NSCLC). Methods: Seventy patients with NSCLC (stage I–III) undergone radical surgery were randomized into two groups: 35 patients received adjuvant chemotherapy with cyclophosphamide (CTX) 300 mg/m^2, vincristine (VCR) 1.4% mg/m^2, adriamycin (ADM) 50 mg/m^2, lomustine (CCNU) 50 mg/m^2 dl, cisplatin (DDP) 20 mg/m^2, d1–5, for 4 cycles, and followed by oral Ftorafur (FT-207) 600–900 mg/d for 1 year (adjuvant chemotherapy group). The other 35 patients received surgical treatment only (surgery group). Results: The overall 5-year survival rate was 48.6% in the adjuvant chemotherapy group, and 31.4% in the surgery group, respectively. The difference between the two groups was not statistically significant (P>0.05). The 5-year survival rate of patients in stage III was 44.0% and 20.8% received surgery with and without adjuvant chemotherapy, respectively. The difference between the two groups was statistically significant (P<0.025). The 5-year survival rate of patients in stage I–II in the two groups was 60.0% and 54.5%, respectively (P>0.75). Conclusion: Postoperative adjuvant chemotherapy in NSCLC can improve survival, for those patients in stage III, it suggests significantly 5-year survival rate in the adjuvant chemotherapy group was higher than that in the surgery alone group.

Key words: Non small cell lung carcinoma, Radical surgery, Adjuvant chemotherapy, Survival rate.

From January 1989 to July 1992, 70 patients underwent radical surgery for non small cell lung cancer (NSCLC) were randomized into group treatment. The results reporting are follows.

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MATERIALS AND METHODS

General Materials

All patients after radical surgery were randomized into two groups: adjuvant chemotherapy group and surgery group. 35 patients received adjuvant chemotherapy, there were 31 males, 4 females; Median age was 55 years (age ranged from 43 to 66 years), Karnofsky performance status was 80 (ranged from 70 to 90). Among them, there were 12 squamous cell carcinomas, 19 adenocarcinomas, 3 squamous-adenocarcinomas, 1 large cell carcinoma; 6 patients were stage I, 4 were stage II, 20 were stage III_a, 5 were III_b. 35 patients received surgical treatment alone, there were 28 males, 7 females; median age was 56 years (ranged from 29 to 68), median Karnofsky performance status was 80 (ranged from 70 to 100). Among them there were 14 squamous, 17 adenocarciomas, 3 squamous-adenocarcinomas, and one large cell carcinoma. 7 patients were stage I, 4 stage II, 20 stage III_a, 4 stage III_b.

Chemotherapy Regimen

Using COAPC regimen consisted of cyclophosphamide (CTX) 300 mg/m^2, vincristine (VCR) 1.4 mg/m^2, adriamycin (ADM) 50 mg/m^2, intravenously respectively d1; cisplatin (PDD) 20 mg/m^2, dissolved in 250 ml of 3% saline iv infusion, d1–5; lomustine (CCNU) 50 mg/m^2, oral, d1, and repeated every 4–6 weeks for 4 cycles. Hereafter, orally administration of Ftorafur (TF-207) 200–300 mg tid for 1-year or until recurrence.

Before chemotherapy, all patients underwent routine physical examination and routine blood tests, liver and renal function tests, chest radiography,

ultrasound scan of the abdomen, Electrocardiogram, and CT or ECT if clinically indicated. Before every therapeutic cycle and end of therapeutic cycle, above examination was repeated. After the beginning of chemotherapy white blood cell count, hemoglobin and platelet count was done weekly. During oral administration of FT-207, routine blood test was done each 2 to 3 weeks, above examination was repeated each 2 months.

Toxicity Criteria

Toxicity of chemotherapy was scored according to WHO criteria.

Statistical Methods

Survival was calculated from the date of surgery. Survival curves was plotted by method of Kaplan-Meier, the Log-Rank test was used to compare intergroup different significance.

RESULTS

Survival Rate

The follow-up was closed on July 1997, 3 patients lost to follow-up after recurrence. The overall (stage I–III) 5-year survival rate was 48.6% and 31.4% in the adjuvant chemotherapy group, and surgery group, respectively, the difference between the two groups was not statistically significant ($P>0.05$). The 5-year survival rate of patients in stage III was 44. 0% in adjuvant chemotherapy group and 20.8% in surgery group, respectively, the difference between these two groups was statistically significant ($P<0.025$). The 5-year survival rate of patients in stage I–II in the two groups was 60.0% and 54.5% respectively ($P>0.75$). 5-year survival rate of patients with squamous in adjuvant chemotherapy group and surgery group was 58.3% and 35.7% respectively. The 5-year survival rate of patients with adenocarcinomas in both groups was 47.4% and 29.4% respectively. Comparison of patients with squamous in both groups, $P>0.25$. Comparison of adenocarcinoma, $P>0.1$; Comparison between squamous and adenocarcinoma in adjuvant chemotherapy group; $P>0.5$; Comparison between squamous, and adenocarcinoma in surgery group, $P>0.75$; There were no all statistical significant. Survival curves of the patients in overall group (stage I-III), stage III and stage I–II are shown in Figure 1, 2 and 3.

Causes of Death

The causes of death in both groups are shown in Table 1. Among dead patients, occurrence rate of brain metastases was higher, which were 61.1% (11/18) and 37.5% (9/24) in adjuvant chemotherapy group and surgery group respectively. There was no statistically significant in causes of death between two groups.

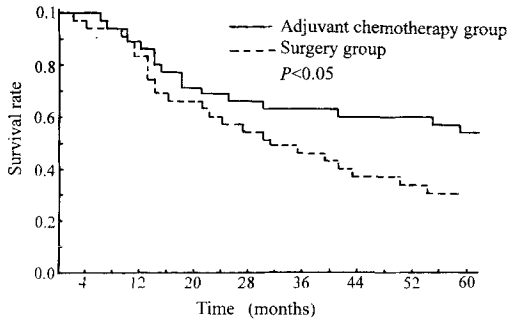

Fig. 1. Overall survival curves of all patients with stage I–III in both groups

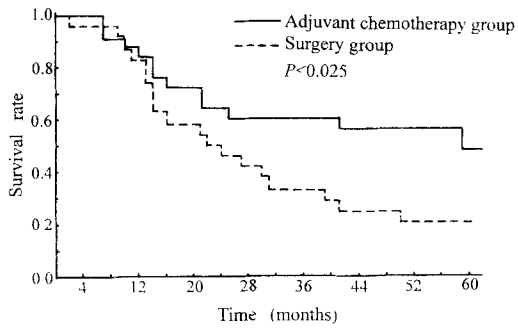

Fig. 2. Survival curves of patients with stage III in both groups

Adverse Effects of Chemotherapy

Nineteen patients had grade I–II are nausea and vomiting, account for 54.3%, 10 patients had grade III–IV, 28.0%. 31 patients had grade I–II leukopenia, account for 88.6%, 11 had grade III–IV, 31.4%. 18 patients had grade I–II hemoglobin decrease, account for 51.4%; one had grade III, 2.9%. 2 patients had grade I–II thrombocytopenia, account for 5.7%. All patients had grade III alopecia, one patients each had dizziness, 4 patients had asthenia, one patients each had stomatitis, abdominal pain, diarrhea and constipation, respectively; 2 patients had skin itch, numb of fingers and toes, respectively. No patients with evidence of myelosuppression were not seen during oral administration of FT-207, a few patients had gastrointestinal tract reaction, but all can be acceptable after dose adjustments and plus oral administration of metoclopramide.

DISCUSSION

The effect of adjuvant chemotherapy after radical surgery for NSCLC has been reported in a great deal of literatures, but there is discrepancy in the conclusion. However, postoperative adjuvant chemotherapy is an important way which can control and eliminate the residual disease and micrometastases.[1,2]

Table 1. Analysis of death causes in both groups

Group	No. of death	Local/regional relapses	Distant Metastases	Local plus distant metastases
Adjuvant chemotherapy group	18	5 (27.8)	9 (50.0)	4 (22.2)
Surgery group	24	9 (37.5)	7 (29.2)	8 (33.3)

Notes: In ( ) is %.

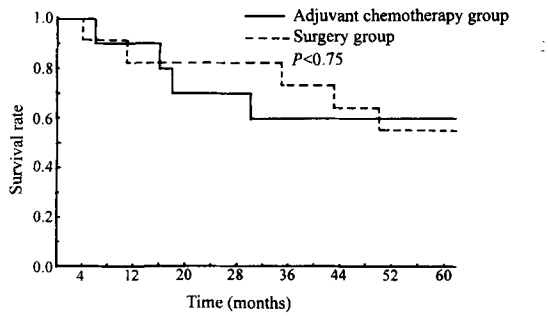

Fig. 3. Survival curves of patients with stage I–II in both groups

The results of this study are similar to that of postoperative combination chemotherapy with CTX, ADM and DDP reported by Niiranen et al.,[3] and is also similar to results of combined chemotherapy with vindesine (VDS) and DDP followed by oral administration of UFT reported by Wada et al.[4] Survival curves of patients with stage III in our study are similar to Figure 1, but after two years, survival curves are obviously divided, there were significant difference ($P<0.025$). This showed that adjuvant chemotherapy is more benefit for the patient with stage III.

Our selected COAPC regimen was referencing to the experience of Takita et al.,[5] the therapeutic effect was raised. After chemotherapy with COAPC regimen, we used oral administration of FT-207 for 1-year, this methods is similar to three courses of VDS plus DDP and 1-year oral administration of UFT reported by Wada et al.,[4] and the results are also similar. The major causes of death of patients with NSCLC in this group are recurrence in thoracic cavity and distant metastases, this is similar to that reported by Niiranen et al., Wada et al.[4]

Mathews et al.[6] reported that the result of study of patients with NSCLC dying within 30 days after curative resection suggested that 13% of the cases had local regional disease and 20% had distant metastases, and metastases in patients with adenocarcinoma is a high as 40%. Pagani et al.[7] found that 30% of patients with stage I and II had adrenal metastases, Mirra et al.[8] during detection of exploratory laparotomy before thoracotomy found that 14% of patients with squamous cell carcinoma had abdominal metastases, and 40% in patients with adenocarcinoma and 30% in cases with large cell carcinoma. The primary tumors of those patients were thought to be surgically resectable. Thus it can indicate that postoperative adjuvant chemotherapy for the patients with NSCLC is extremely necessary.

This result suggested that postoperative adjuvant chemotherapy in NSCLC can improve survival only in patients in stage III, it indicate that there was a higher 5-year survival rate in the adjuvant chemotherapy group comparing with the surgery alone group, further study is worthy.

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DETECTION OF GENE MUTATION IN SPUTUM OF LUNG CANCER PATIENT

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Lung cancer is a common malignant tumor, which has a high incidence and mortality rate. Therefore, it is necessary to seek a new method for the diagnosis, especially the early diagnosis of lung cancer. The development of molecular biology makes the gene diagnosis of lung cancer possible. PCR-SSCP was applied to detect p53 gene mutation of lung cancer patients' sputum cells and we have achieved good results.

MATERIALS AND METHODS

Third-six lung cancer inpatients in the Second Hospital Affiliated to the Fourth Military Medical University were chosen, among whom were 24 males and 12 females with a average age of 58±8.2 (41~72). According to TNM differential criterion, there were 14 patients with stage II lung cancer and 22 with stage III lung cancer. And there were 18 patients with squamous cell cancer, 12 with adenocarcinoma, 4 with small cell lung cancer and 2 with large cell lung cancer. Samples were taken from the patients' resected fresh lung cancer tissues. Sputa were collected before operation (1~2 mouthful/day, 3 days altogether). And there were 20 controls groups, whose samples were the normal lung tissues resected with lung cancer mass as well as sputa taken from pneumonia and bronchitis patients. DNA were extracted with saturated phenol-chloroform and ethanol precipitated. PCR-SSCP was conducted (p53 primers were aimed at exon 5~8 of p53 and were composed by Shanghai Biochemistry Institute of Chinese Academy of Sciences). Sputa were washed and centrifugalized with normal saline for three times. After the sediment was smeared and dyed, common sputum cytology detection was conducted under light micros-cope.

RESULTS

Of the 36 lung cancer patients, 19 were detected to have p53 mutation in severed lung cancer tissues (stage II 6, stage III 13), with a positive rate of 52.78%, and 15 were detected to have p53 mutation in sputa with a 41.67% positive rate and all the 15 patients were also among the former 19 patients. To those patients who had p53 mutation in tissues, the positive rate of sputum cell gene mutation detection with PCR-SSCP was 78.95%, and 55.56% (20/36) for common sputum cytology detection. No p53 gene mutation was detected in tissues or sputa of control samples.

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DISCUSSION

The genesis of lung cancer is related to many kinds of oncogenes and suppressor genes. The diagnosis of lung cancer can be conducted by detecting these genes. About 60% of lung cancer patients were found to have p53 gene mutation. This kind of mutation is mainly point mutation, whose site is mainly in exon 5~8. PCR-SSCP is commonly used to detect gene mutation at present. It is sensitive, comparatively simple and able to detect many samples simultaneously. The detection of the resected lung cancer tissues showed that over 50% of the lung cancer patients had p53 gene mutation, which suggested that the p53 mutation is common in lung cancer. However, the detection of the gene mutation in resected tissues of lung cancer is not applicable to the clinical diagnosis before operation and non-operative patients, and has little significance in practical clinical diagnosis. Sputum cytology detection is commonly used in the diagnosis of lung cancer, which is easy to operate and collect samples but not so sensitive. PCR could be used to detect the very few cancer cells in the sputa of lung cancer patients, thus improving the sensitivity of sputum cytology detection. In this study, the p53 gene mutation of sputum cells was detected with PCR-SSCP and the total positive rate was 41.67%, lower than that of common sputum cytology detection. But of those 19 patients who had p53 muta-tions in lung cancer tissues, the positive rate of sputum detection with PCR-SSCP was 78.95%, obviously higher than that of common sputum cytology detection ($P<0.01$). The positive rate of PCR-SSCP was low mainly because the p53 gene mutation rate in lung cancer is not high enough as well as the defect of the method itself.