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Neoadjuvant chemotherapy and concomitant boost radiotherapy in locally advanced non-small cell lung cancer

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ABSTRACT

This Phase II study was designed to assess the possibility of increasing local control and decreasing distant metastasis by using neoadjuvant chemotherapy, and concomitant boost radiotherapy which was used to prevent accelerated repopulation in locally advanced non-small cell lung cancer. Thirty-one patients with stage IIIA and IIIB non-small cell lung cancer were included into this phase II study. Two cycles neoadjuvant cisplatin and vinorelbine were applied. This was followed by thoracic radiotherapy of 64.4 Gy. Response evaluation was performed 4 weeks after the radiotherapy. One year overall survival, progression-free survival and distant disease-free survival rates were 38.4%, 42.1% and 65%, respectively. An objective response was observed in 75% of patients. Different doses of cisplatin affected objective response rate and distant disease-free survival. Grade 3-4 toxicities occurred in 17 patients with chemotherapy and 9 patients with radiotherapy. There was no late grade 3-4 toxicity. Neoadjuvant chemotherapy and concomitant boost accelerated radiotherapy seems difficult to be considered as a standard treatment method. The ratio of objective response and survival is not at desirable level even though it is higher than the conventional technique. [Turk J Cancer 2006;36(4):162-168].

KEY WORDS:

Non-small cell lung carcinoma, neoadjuvant chemotherapy, accelerated radiotherapy, toxicity, survival

INTRODUCTION

Lung cancer is the second most fatal and common cancer type which is followed by prostate cancer in men and breast cancer in women (1,2). For locally advanced inoperable stage III non-small cell lung cancer (NSCLC), daily fractioned thoracic radiotherapy (RT) has been mainstay of treatment until early 1990s. The successful treatment of locally advanced NSCLC depends on the control of both clinically apparent intrathoracic disease and occult systemic micrometastasis commonly present at the time of diagnosis. Therapeutic regimen with RT alone fails to achieve these goals in more than a minority of patients (3,4).

In randomized studies, it is reported that neoadjuvant chemotherapy (Cht) reduces distant metastasis rates and increases survival rates with acceptable toxicity (5-7). Based on this information, this study aims to reduce the possible development of distant metastasis and decreasing the size of tumor with the help of neoadjuvant cisplatin-vinorelbine Cht in case of locally advanced stage NSCLC.

MATERIALS AND METHODS

Between July 1999 and August 2001, 31 patients with NSCLC were included in this prospective phase II study in our department. The study was performed after approval

was obtained from the institutional ethics committee and informed consent was obtained from all patients.

Eligibility criteria included: histological proof of NSCLC, considered non-operable in surgical consultation, age < 70, Karnofsky performance score (KPS) > 60, no previous antineoplastic therapy, body weight loss of less than 15% during the previous 3 months, 1 liter or more FEV, without any distant metastasis, malignant pleural and pericardial effusion, and having no medical difficulties to receive Cht were involved in our study. Patients with superior sulcus tumors and vena cava superior syndrome were not accepted because of their different prognostic characteristics. The characteristic of patients are listed in table 1.

Table 1
Patient characteristics

Characteristics	n	%
Age		
≤60	12	38.8
>60	19	61.2
Gender		
Male	29	93.5
Female	2	6.5
Karnofsky performance status		
60-80	17	54.8
90-100	14	45.3
Weight loss		
5-15%	18	58
<5%	13	42
Symptoms		
Cough	21	68
Sputum	11	35
Chest Pain	14	45
Dyspnea	8	26
Hemoptysis	7	23
Tumor size		
<5 cm	10	32.2
>5 cm	21	67.8
AJC Stage		
Stage IIIA	10	32.3
T2N2	3	9.7
T3N2	7	22.6
Stage IIIB	21	67.7
T3N3	1	3.2
T4N0	9	29
T4N2	8	25.8
T4N3	3	9.7
Histology (WHO)		
Epidermoid carcinoma	26	84
Adenocarcinoma	5	16

Two cycles of neoadjuvant Cht were applied by giving cisplatin on days 1 and 22, and vinorelbine on days 1, 8, 22 and 30. The dose of cisplatin given to the first 18 patients was 75 mg/m^2, and given to the next 13 patients was 100 mg/m^2. The dose of vinorelbine for both groups was 30 mg/m^2.

Twenty-four patients were included in this concomitant boost accelerated RT. Chest irradiation began 2 weeks after the completion of Cht. RT was delivered to the primer tumor, ipsilateral hilum, and mediastinum with 2 cm margins. Tumor volume definition was based on preinduction chemotherapy tumor volume. The contralateral hilum and mediastinum were included with a 1 cm margins. If they were grossly involved, the margins were 2 cm. The ipsilateral supraclavicular fossa was included only for upper lobe tumors or if it was clinically involved. This initial volume was treated to a total tumor dose of 50 Gy in 25 fractions of 2 Gy over 5 weeks. The boost volume consisted of the primary tumor with 2 cm margins and was taken to an additional dose of 14.4 Gy in 8 fractions of 1.8 Gy. The total dose to the tumor was 64.4 Gy, and the total treatment time was 5 weeks, because the treatment to the boost volume was delivered concomitantly with the last 8 days of large volume, with an interval of at least 6 hours between treatments. Patients were treated with cobalt-60 teletherapy machine (Theratronics, Theratron 780-C).

Objective response was evaluated with computerized tomography (CT) scan of the chest. Objective response to chemotherapy was assessed at one week after completion of chemotherapy regimen. Objective and symptomatic response to RT was assessed at fourth week after the last day of RT. An objective response was defined a 50% or greater decrease of all objective disease. Stable disease was defined as less than a 50% regression. Symptomatic response was evaluated with physical examination and questioning, and it was thought that there was a response if reduction is more than 50%, and there was no response if it is less than 50%.

Weekly Cht toxicities were assessed by using Common Toxicity Criteria (CTC) (8). RT toxicities were graded by using Radiation Therapy Oncology Group (RTOG) criteria (9). In the controls every week during RT, every month in the first 6 months after the treatment and every two months, patients were evaluated. Side effects which were observed in the first 3 months following the treatment were considered to be acute, and those observed after the first 3 months to be late toxicity.

Rates for overall survival, local progression-free survival, and distant disease-free survival were calculated from the last day of RT by the method of Kaplan-Meier. The log rank test was used to analyse the effect of different chemotherapy doses on overall survival, local progression-free survival, distant disease-free survival and RT response (10). All p values were two-tailed; a value of 0.05 or less was considered significant.

RESULTS

Twenty-four patients completed the treatment plan. Six patients left the group on their own wishes because of grade 3 vomiting problems appeared after the first cure of Cht. One patient died of lung infection developed after the second cure of Cht. Twenty-four patients whose findings were evaluated were observed for 8 months on median (range: 2-29 months). Of the 24 patients, 13 have died and 11 patients were alive.

After completion of the chemotherapy there was 9 objective response (38%) and 18 objective response (75%) after RT. Thus, the mean ratio of response is 75%. Hemoptysis was the symptom through which the best response rate of 100% was obtained. The other symptoms following hemoptysis were pain with 91%, sputum 83%, dyspnea 80% and coughing 56%.

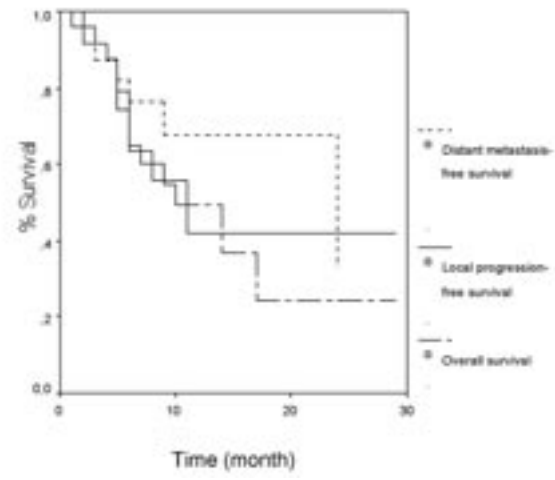

Fig 1. Overall, local progression-free and distant metastasis-free survival

Table 2
Chemotherapy toxicity (CTC)

Toxicity	Grade 1-2 n	Grade 3-4 n
Hematologic		
Anemia	8	0
Neutropenia	5	9
Gastrointestinal		
Nausea - vomiting	11	8
Kidney	5	0

Table 3
Radiotherapy toxicity (RTOG)

Toxicity	Grade 1-2 n	Grade 3-4 n
Acute Toxicity		
Skin	21	0
Esophagitis	20	4
Nausea - vomiting	13	0
Neutropenia	2	0
Anemia	8	0
Thrombocytopenia	1	0
Pneumonitis	15	5
Late Toxicity		
Skin	10	0
Esophagitis	4	0
Pulmonary fibrosis	7	0

The median overall survival time of 24 patients in our group was 11 months (range 2-29 months) with 38.4% of the patients alive at the end of first year (Figure 1). The one year local progression-free survival rate was 42.1%, with a median progression-free survival time of 10 months (Figure 1). The one-year distant disease-free survival was 65% and median distant disease-free survival time was 24 months (Figure 1).

72.2% objective response was found in the group who received 100 mg/m^2 cisplatin and 77% objective response in the group who received 75 mg/m^2, the difference was significant (p=0.03). When the two groups were compared with respect to one year distant metastasis-free survival, in the group who had 100 mg/m^2 cisplatinum is 100%, and in the group who had 75 mg/m^2 cisplatinum is 47%, the difference was significant (p=0.01).

Severe toxicity during Cht are shown in table 2. Patients suffered from late and early RT toxicity are listed in table 3.

DISCUSSION

The outcome of conventional thoracic irradiation alone in locally advanced disease is not satisfactory, with a 5-year survival rate of less than 10% (4,11), but still plays a definite palliative role (12-14). RTOG conducted a phase I/II concomitant boosted RT in locally advanced NSCLC and long-term results show that the median survival is 10 months, and point out that 1 and 5 year survival rates are 41%, 4%, respectively, and eventually acceptable late toxicity was found (15). In the study of CALGB (Cancer and Leukemia Group B) comparing standard RT and two cycles of neoadjuvant Cht combining cisplatin and vinblastin and standard RT, while no statistical difference was found among local control rates (56% against 43%), the difference among median periods was found to be statistically significant (13.8 months versus 9.7 months). One and two-year survival rates in neoadjuvant cht arms were 54% and 26%, respectively (6,16).

Although some hopeful early results were found in the study of RTOG which makes inquiries concerning concomitant chemotherapy and hyperfractioned RT, and consecutive concomitant chemotherapy and standard RT, and neoadjuvant chemotherapy combining cisplatin, vinblastin and oral etoposide and standard RT, no statistical difference among three groups was found in terms of local control and survival period, and acute and late side effects were increased significantly in hyperfractioned and concomitant treatment arms (17).

The relationship between cisplatin dosage and survival is not clear yet. The patients who had response in randomized studies show that dosage has an important role on response period and survival. Cisplatinum dosage varies 60 mg/m^2 to 120 mg/m^2 in combined chemotherapy regimens (18,19). In our study, the rates of response and survival were investigated in two different cisplatin dosages; the group that received 75 mg/m^2 dose had better objective results, and the group that received 100 mg/m^2 had better result of distant metastasis-free survival. The difference between groups was statistically significant. However, overall survival rate found in the group received 100 mg/m^2 and one-year locally progression-free survival rate in the group received 75 mg/m^2 cisplatin were higher than the other group, and the differences were not statistically significant. Thus, it can be concluded that cisplatin dosage impeding metastasis development contributed to distant disease-free survival.

When median survival and local control rates in our study are compared to those in CALGB and RTOG, median survival periods were similar, local control and one year survival rates were found lower. In comparison with the study of Viallet et al. (20), while rates of objective response and overall progression-free survival rates are similar, overall survival rates are lower. In general, rates we obtained are better than those of standard fraction RT (21,22).

In our study, grade 3 vomiting originated from Cht appeared in 14 out of 31 patients in spite of prophylactic antiemetic regimen of 5 HT3 receptor antagonist; and this caused the adaptability problem in the patients; so six patients gave up the treatment on their own desires.

Parenteral supportive treatment apart from antiemetic was applied to 8 out of 24 patients who developed vomiting problem after the completion of Cht. Grade 3-4 early RT toxicity was found in 9 patients; as esophagitis in 9 patients and as radiation pneumonitis in 5 patients. Nevertheless, RT was completed with the help of supportive medicine treatment without any interruption. Grade 3-4 late toxicity did not appear in median 10 months (range 2-29 months) follow-up. It has been thought that neoadjuvant Cht increases the acute radiation toxicity and decreases the toleration towards RT.

Objective response rate and the rates of one-year overall, local progression-free and distant disease-free survival in our study seem higher than conventional techniques; Grade 3-4 gastrointestinal toxicity due to Cht was found higher; this phenomenon decreases the toleration of patient and makes adaptation more difficult. The level of acute and late grade 3-4 RT toxicity is tolerable. However, neoadjuvant Cht increases acute toxicity connected with radiation and decreases toleration towards RT. The time required for RT may put those patients at a disadvantage, especially when they fail to demonstrate satisfactory responses after the neoadjuvant Cht.

Although the number of patients in our study was low, our results are better than conventional fractionated RT but not than concomitant boost RT (15). And the toxicity rates are high. Based on our results, it is difficult to say that neoadjuvant Cht by concomitant boost RT is better and tolerable than the concomitant boost RT (15).

CONCLUSION

Neoadjuvant Cht followed by concomitant boost accelerated RT seems difficult to be considered as a standard treatment method. The ratio of objective response and survival is not at desirable level even though it is higher than the conventional technique. Further studies are needed to improve the rates involving new therapy modalities and the combinations.

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