Hyperfractionated Radiotherapy and Concurrent Chemotherapy for Stage III Unresectable Non Small Cell Lung Cancer : Preliminary Report for Response and Toxicity

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=Abstract=

Lung cancer study group at Asan Medical Center has conducted the second prospective study to determine the efficacy and feasibility of MVP chemotherapy with concurrent hyperfractionated radiotherapy for patients with stage III unresectable non-small cell lung cancer(NSCLC).

All eligible patients with stage III unresectable NSCLC were treated with hyperfractionated radiotherapy(120 cGy/fx BID, 6480 cGy/54fx) and concurrent 2 cycles of MVP(Mitomycin C 6mg/m^2, d2 & d29,Vinblastine 6mg/m^2, d2 & d29, Cisplatin 60mg/m^2, d1 & d28) chemotherapy. Between Aug. 1993 and Nov. 1994, 62 patients entered this study; 6(10%) had advanced stage IIIa and 56(90%) had IIIb disease including 11 with pleural effusion and 10 with supraclavicular metastases.

Among 62 patients, 48(77%) completed planned therapy. Fourteen patients refused further treatment during chemoradiotherapy. Of 46 patients evaluable for response, 34(74%) showed major response including 10(22%) with complete and 24(52%) with partial responses. Of 48 patients evaluable for toxicity, 13(27%) showed grade IV hematologic toxicity but treatment delay did not exceed 5 days. Two patients died of sepsis during chemoradiotherapy. Severe weight loss(more than 10%) occurred in 9 patients(19%) during treatment. Nine patients(19%) developed radiation pneumonitis. Six of these patients had grade I (mild) pneumonitis with radiographic changes within the treatment fields. Three other patients had grade II pneumonitis, but none of these patients had continuous symptoms after steroid treatment. Concurrent chemoradiotherapy for patients with advanced NSCLC was well tolerated with acceptable toxicity and achieved higher response rates than the

first study, but rather low compliance rate(77%) in this study is worrisome. We need to improve nutritional support during treatment and to use G-CSF to improve leukopenia and if necessary, supportive care will be given as in patients. Longer follow-up and larger sample size is needed to observe survival advantage.

Key Words : Non-Small Cell Lung Cancer, Concurrent Chemoradiotherapy

INTRODUCTION

The incidence of lung cancer has been rapidly increasing in Korea as in the world. However the majority of patients are diagnosed as advanced stage III and IV disease. The 5 year survival of patients with unresectable, locally advanced NSCLC is approximately 5% using conventional radiation therapy alone[1].

Although significant proportion of unresectable NSCLC patients develop distant metastases during their course of disease, intrathoracic failure remains as an important cause of death for these advanced stage patients[2]. Current clinical research efforts are, in part, directed at decreasing local failure, which it is hoped will translate into an improvement in long term survival. One approach has been the use of multiple daily fractionations. Phase I/II trial of hyperfractionation in advanced NSCLC aimed at finding the highest total dose with acceptable acute and late morbidity and examining the effect of increasing total dose on local tumor control were performed. RTOG[3] study demonstrated acceptable acute and late toxicity at all total doses tested up to 79.2 Gy, and a survival advantage for favorable patients with stage III disease who received 69.6 Gy in 1.2 Gy twice daily fractions. This group had a 13 months median survival and a 29% 2 year survival.

Given the presence of micrometastatic disease, effective systemic therapy should improve survival in stage III NSCLC. Although generally ineffective in stage IV or recurrent disease, studies using various combinations of drugs in stage III disease have generated response rates as high as 73%, when used prior to definitive local treatment[5]. The CALGB trial reported that induction chemotherapy combined with radiation therapy increased survival in phase III trial[6].

From January 1991 to July 1993 we conducted a prospective randomized study of induction MVP chemotherapy followed by hyperfractionated radiotherapy and randomization of maintenance chemotherapy for stage III unresectable NSCLC. In this study the combination of mitomycin C, vinblastine, and cisplatin produced a response rate of 58 percent in unresectable stage III patients[4] and responders of induction chemotherapy showed better survival than non-responders. Adjuvant chemotherapy group showed statistically significantly better survival than observation group. Although this our previous study produced a high rate of locoregional response and the 1 and 2 year survival, adjuvant chemotherapy group consumed 8 months of their life for the therapy, so we thought it is important to shorten the treatment time for the quality of life.

Based on the 1st study, we conducted the 2nd study of hyperfractionated radiotherapy with concurrent 2 cycles of MVP chemotherapy for unresectable stage III NSCLC from August 1993. The objectives of this preliminary report are to determine the response rates and acute toxicity of concomitant chemoradiotherapy.

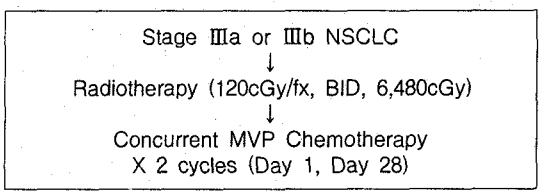

Fig. 1. Study design for locally advanced non- small cell lung cancer.

Table 1. Patient Characteristics

(1993. 8-1994. 11)

Characteristics	No. of Patients (%)
Age, years	
Median	59
Range	40 - 72
Sex	
Male	57 (92)
Female	5 (8)
Stage	
IIIa	6 (10)
IIIb	56 (90)
Pathology	
Squamous ca	41 (66)
Adeno ca	11 (18)
Undetermined	7 (11)
Large cell ca	3 (5)

Table 2. TNM Stage of The Patients

	T1	T2	T3	T4*	Total
No				7	7
N1				0	0
N2		3	3	16	22
N3#	2	10	8	13	33
Total	2	13	11	36	62

* 11 Patients had pleural effusion
# 10 Patients had supraclavicular mets

MATERIALS AND METHODS

Patients with stage III unresectable NSCLC were treated with hyperfractionated radiotherapy with concurrent 2 cycles of MVP chemotherapy (Fig. 1). All patients without evidence of distant metastases were included. Patients with involvememt of supraclavicular lymph nodes or cytologically negative pleural effusions were included. The eligible patients were reviewed by a medical and radiation oncologists and pulmonologists prior to treatment assignment. All patients had pathologically documented NSCLC, including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Radiologic evaluation consisted of chest X-ray, bone scan and chest CT including upper abdomen. Laboratory studies required at entry included a leukocyte count higher than 4000 per mm^3, platelet count higher than 10^5 per mm^3 and blood urea nitrogen, creatinine and bilirubin levels less than 1.5 times than upper range of normal value.

Table 3. Leukopenia during Treatment

Grade	No. of Patients (%)	
	1st Chemo	2nd Chemo
1 (3-4000)	7(15)	7(15)
2 (2-3000)	9(19)	13(27)
3 (1-2000)	10(21)	11(23)
4 (< 1000)	4(8)	9(19)*
Total(Gr 3-4)	14/48 (29)	20/48 (42)

*: 2 pts expired of pneumonia

Radiation therapy was started with large and boost volumes sequentially. The large treatment volume included the primary lesion with a 2cm margin, the ipsilateral hilar and mediastinal lymph nodes from the thoracic inlet to 5cm below the carina. The inferior mediastinum was included when lesions were located in the lower lobe. The ipsilateral supraclavicular fossa was included. The boost volume included the primary tumor and the involved nodal lesions with a margin of no more than 2cm. The dose to the original volume was 4,320 cGy in 36 fractions of 120 cGy BID. Minimum 6 hour interval was given between two daily treatments. The dose to the boost volume was 2,160 cGy in 18 fraction of 120 cGy BID. The total tumor dose was 6,480 cGy and the maximum dose to any point along the spinal cord was 4,500 cGy.

Chemotherapy consisted of mitomycin C (6 mg/m^2 given IV on day 2,29), vinblstine (6mg/m^2 given IV on day 2,29), and cisplatin (6mg/m^2 given IV over 3 hours with hydration on day 1,28). The doses were modified on the basis of blood counts and tests of renal and hepatic function on the day of therapy.

Response was assesed one month after the completion of chemoradiotherapy by chest CT. A complete remission was defined as the disappearance of the tumor by CT scan. A partial remission was defined as a reduction of more than 50 percent of measurable disease and no response as a reduction of less than 50 percent.

Table 4. Radiation Pneumonitis Grading System

(SWOG Criteria)

Grade	Symptoms and Findings
1 (mild)	Radiographic changes (Chest X ray or CT) and Clinical symptom exist but do not require steroids
2 (moderate)	Steroids are rquired
3 (severe)	Oxygen is needed
4 (life-threatening)	Assisted ventilation is necessary

Table 5. Locoregional Response after Chemoradiotherapy

	No. of Patients (%)
CR	10 / 46 (22)
PR	24 / 46 (52)
NR	4 / 46 (9)
PD	8 / 46 (17)

RESULTS

Sixty two patients were registered to this study until Nov. 1994. The characteristics of these patients are shown in table 1 and 2. The median age was 59 years with a range of 40 to 72 years. Six(10%) had advanced stage Ⅲa and 56(90%) had Ⅲb diease including 11 with pleural effusion and 10 with supraclavicular L/N metastases.

Among 62 patients, 14 refused treatment during the radiotherapy after the 1st cycle of chemotherapy, so 48 patients (77%) completed planned therapy. Of 48 patients evaluable for toxicity, 13 (27%) showed grade Ⅳ hematologic toxicity (Table 3), but treatment delay did not exceed 5 days. Two patients died of sepsis during chemoradiotherapy. Radiation pneumonitis was scored by SWOG scoring system(Table 4). Nine patients (19%) developed radiation pneumonitis. Six of these patients had grade Ⅰ pneumonitis with radiographic changes within the treatment fields. Three other patients had grade Ⅱ pneumonitis, but none of these patients had continuous symptoms after steroid treatment. Severe weight loss (more than 10%) occurred in 9 patients (19%) during treatment.

Of 46 patients evaluable for response, 34 (74%) showed major response including 10 (22%) with complete and 24 (52%) with partial responses (Table 5).

DISCUSSION

This study is based on our previous study of hyperfractionated radiotherapy following induction chemotherapy for stage Ⅲ NSCLC and randomization for adjuvant chemotherapy vs. observation. The response rates of MVP induction chemotherapy were 58% and the responders with induction chemotherapy showed better survival than non-responders. Sixty five percent of patients showed more than partial response with induction chemotherapy and sequential radiotherapy. There are numerous combination chemotherapy regimens currently in use, particularly cisplatin based regimens seem to produce the improved response rates compared with no platinum based regimens. Mitomycin C, vinblastine, and cisplatin combination chemotherapy has produced response rates of 30% to 70%[7,8]. In our previous study, MVP chemotherapy showed 58% of response rates and did not increase complication rates compared with radiotherapy alone group. Therefore we have continued to use MVP chemotherapy in this study.

In this study, we delivered hyperfractionated radiotherapy for NSCLC. A phase Ⅰ/Ⅱ trial of hyperfractionated radiotherapy for NSCLC by RTOG showed that survival with 69.6 Gy (median 13 months, 29% of 2 year survival) was significantly ($p=0.02$) better than that of lower total dose. We selected a total dose of 64.8 Gy to avoid co-toxicity of concurrent chemoradiotherapy.

Response rates of 74% with concurrent chemoradiotherapy is significantly superior result compared with 65% of previous study after sequential chemotherapy and radiotherapy. Although our study included more advanced stage patients with involvement of ipsilateral or contralateral supraclavicular lymph nodes and pleural effusion, this

regimen produced a high rate of locoregional response compared to the most active multimodality regimens reported in locally advanced NSCLC[9, 10].

The toxicity of MVP chemotherapy with concurrent radiotherapy was unknown to us at the inception of this study. Leukopenia of grade 3 and 4 occurred in 14 of 48 patients (29%) after 1st cycle of chemotherapy and 20 of 48 (42%) after 2nd cycle of chemotherapy. Two patients with grade 4 leukopenia died of septicemia. Six patients (19%) suffered severe (more than 10%) weight loss during treatment but recovered 1 or 2 weeks after the completion of treatment. Incidence of radiation pneumonitis was lower than that of other historical control groups. Three patients complained grade 2 radiation pneumonitis with severe cough and mild dyspnea one month after treatment, but none of these patients had continuous symptoms after steroid treatment. Although longer follow up period and more number of patients are needed to determine survival advantage and late complication rates, authors are encouraged with higher response rates and acceptable toxicity of this treatment.

In conclusion, a combination of concurrent radiotherapy and chemotherapy in patients with advanced NSCLC was accomplished with acceptable toxicity and higher response rates, therefore we think it is necessary to continue this study. One problem is low compliance rate(77%) of this study, so if necessary, we will do hospitalization during treatment for nutritional support and use of G-CSF to improve leukopenia and to prevent treatment delay.

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=국문초록=

절제 불가능한 제 3기 비소세포성 폐암의 다분할 방사선 치료와 MVP 복합 항암요법의 동시 치료에 대한 예비적 결과

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목 적 : 절제 불가능한 제 3기 비소세포성 폐암에서 다분할 방사선 치료와 MVP 복합 항암요법의 동시 치료에 의한 종양관해율, 급성부작용, 생존기간에 미치는 효과를 알아보기 위하여 1993년 8월부터 전향성 연구(Prospective study)를 시작하였다.

방 법 : 본 연구는 제 Ⅲ기의 비소세포성 폐암중 절제가 불가능한 환자를 대상으로 하여 다분할 방사선치료 (120 cGy/fx, BID)를 6,480 cGy 시행하며 동시에 방사선치료 제1일과 28일에 2회의 MVP (Mitomycin C 6mg/m^2, Vinblastine 6mg/m^2, Cisplatin 60mg/m^2) 복합 항암 요법을 시행하였다. 1994년 11월까지 등록된 62명의 환자에 대한 분석을 시행하였다. 병기는 Ⅲa 환자가 6명이고 나머지 56명은 Ⅲb 환자였으며 이중 흉막액이 있었던 환자는 11명, 쇄골상 임파선 전이가 있었던 환자는 10명으로 대부분의 환자가 Ⅲb 중에서도 진행된 환자였다. 조직학적 유형은 편평 상피암이 41명으로 66% 선암도 11명으로 18%를 차지하였다.

결 과 : 62명의 환자중 끝까지 치료를 마친 환자는 48명으로 이 study의 compliance는 77%이었다. 48명의 환자중 2명은 치료중 치료와 관계된 백혈구 감소로 인한 폐렴으로 사망하였다. 치료의 효과를 판정할 수 있었던 46명의 환자중 완전 관해(CR)는 10명으로 22%의 높은 완전 관해율을 보였다. 부분 관해(PR)는 24명 (52%) 으로 다분할 방사선 치료와 동시 병행 MVP 항암요법에 의한 부분관해 이상의 관해율은 74% 이었다. 급성부작용 판정이 가능했던 46명중 가장 빈도가 높은 급성 부작용은 백혈구 감소로 1차 항암요법후 10명이 Grade 3, 4명이 Grade 4의 백혈구 감소를 보였으며 2차 항암요법에는 11명이 Grade 3, 9명이 Grade 4의 백혈구 감소를 보여 치료기간이 3일에서 5일 정도 지연되는 결과를 나타냈고 이중 2명은 폐렴으로 인한 패혈증으로 사망하였다. 치료중 체중감소를 보인 환자는 26명 (54%) 이었으며 이중 9명에서는 치료전에 비해 10% 이상의 체중감소를 보였다. 치료 1개월후 찍은 CT상 6명에서는 Grade 1의 방사선 폐렴이 관찰되었고 3명에서는 Grade 2로 Steroid 치료후 호전되었다.

결 론 : 이상의 결과 다분할 방사선 치료와 MVP 항암요법의 동시 치료가 이전의 항암요법후 다분할 방사선 치료하는 Sequential 방법에 비하여 높은 관해율을 보이고 특히 22%의 높은 완전 관해율이 관찰되어 이 연구를 계속 진행함으로써 더 좋은 결과를 얻을 것으로 생각되며 급성 부작용에 대하여는 입원을 통한 Nutrition support와 G-CSF 등을 이용하여 백혈구 감소를 막을 수 있을 것으로 생각된다.