MVP Chemotherapy and Hyperfractionated Radiotherapy for Stage III Unresectable Non-Small Cell Lung Cancer

— Randomized for Maintenance Chemotherapy vs. Observation; Preliminary Report —

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To evaluate the effect of MVP chemotherapy and hyperfractionated radiotherapy in Stage III unresectable non small cell lung cancer (NSCLC), authors have conducted a prospective randomized study since January 1991. Stage IIIa or IIIb unresectable NSCLC patients were treated with hyperfractionated radiotherapy (120 cGy/fx BID) up to 6500 cGy following 3 cycles of induction MVP (Mitomycin C 6 mg/m^2, Vinblastine 6 mg/m^2, Cisplatin 60 mg/m^2) and randomized for either observation or 3 cycles of maintenance MVP chemotherapy. Until August 1991, 18 patients were registered to this study. 4 cases were stage IIIa and 14 were stage IIIb.

Among 18 cases 2 were lost after 2 cycles of chemotherapy, and 16 were analyzed for this preliminary report. The response rate of induction chemotherapy was 62.5%; partial response, 50% and minimal response, 12.5%. Residual tumor of the one partial responder was completely disappeared after radiotherapy. Among 6 cases who were progressed during induction chemotherapy, 4 of them were also progressed after radiotherapy.

All patients were tolerated BID radiotherapy without definite increase of acute complications, compared with conventional radiotherapy group. But at the time of this report, one patient expired in two month after the completion of the radiotherapy because of treatment related complication. Although the longer follow up is needed, authors are encouraged with higher response rate and acceptable toxicity of this treatment. Authors believe that this study is worthwhile to continue.

Key Words: NSCLC,. MVP chemotherapy, Hyperfractionated radiotherapy

INTRODUCTION

The incidence of NSCLC continues to increase in KOREA and is the second most common cancer in Korean man. Unfortunately, the majority of patients have advanced stage (III & IV) at the time of diagnosis. Renewed effort to expand the use of surgical resection may prove to be useful for some advanced cases, but radiation therapy is the mainstay of treatment for most of these patients but long term survival after radiation therapy alone is rare. Clinical[1] and autopsy studies[2] suggested local tumor progression as an important element leading to death in advanced stage NSCLC patients.

Radiation Therapy Oncology Group (RTOG) conducted a phase I/II trial of higher total doses administered in fractions of 1.2 Gy twice daily, 10 fractions per week, to a total of 69.6 Gy in six weeks: median survival for the stage III patients were 13 months with one and two year survival rates of 56% and 29% respectively[3]. The frequent appearance of distant metastasis in patients with locally advanced NSCLC has raised the interest in developing an effective systemic treatment.

A large number of clinical trials to explore the efficacy of combination chemotherapy has been conducted. Some recent reports have been cautiously optimistic about its efficacy with the higher "response rate" of newer combination of drugs. Induction chemotherapy combined with radiation therapy has been reported to have increased survival in a phase III trial of the Cancer and Leukemia Group B (CALGB84-33)[4]. Authors have conducted a prospective randomized study to evaluate the effect of induction MVP chemotherapy and hyperfractionated radiotherapy in NSCLC since January 1991. In this study we also attempt to evaluate the efficacy of maintenance MVP chemotherapy.

MATERIALS AND METHODS

The eligibility of the patients was determined by a medical and radiation oncologist before treatment assignment. The patients had pathologically documented non small cell lung cancers, including squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Radiologic evaluation consisted of chest x-ray, bone scanning and computerized axial tomography of the chest and upper abdomen, including the adrenals.

A performance status of 0 to 2 was required. 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 $1\frac{1}{2}$ times than upper range of normal value.

Fig. 1 shows the schema of our study. Stage IIIa or IIIb unresectable NSCLC patients are registered to this study after initial baseline work up. Chemotherapy consists of Mitomycin C (6 mg/m^2 given IV and day 1), Vinblastine (16 mg/m^2 given IV on day 1) and Cisplatin (60 mg/m^2 IV over 3 hours with hydration on day 1). The doses are modified on the basis of blood counts and tests of renal and hepatic function on the day of therapy. Radiation therapy is started in 3 weeks after the completion of chemotherapy.

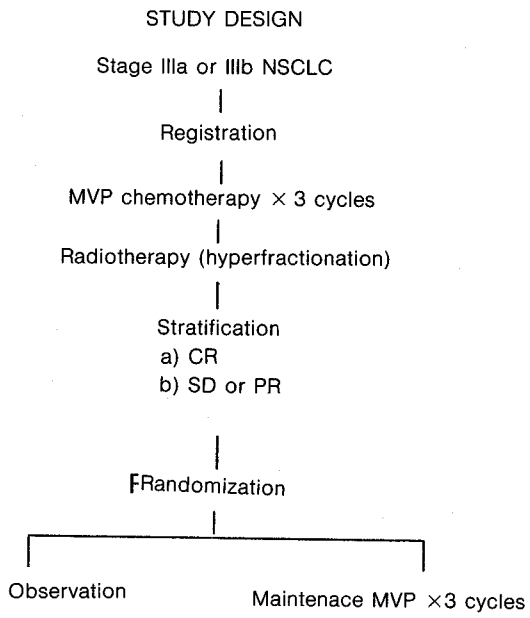

Fig. 1. Study design for locally advanced NSCLC.

The original treatment volume is based on x-ray films and CT scan taken before cytotoxic therapy. The original volume includs the primary lesion with a 2 cm margin, the ipsilateral pulmonary hilum and an inferior margin that extended either 5 cm below the carina or 2 cm below the inferior border of visible tumor. The ipsilateral supraclavicular fossa is included. The boost volume includs the primary lesion before therapy with a 2 cm margin. The dose to the boost volume is 2160 cGy in 18 fractions of 120 cGy BID. The total tumor dose is 6480 cGy and the maximal dose to any point along the spinal cord is 45 Gy. One month after radiotherapy we randomize the patients for either observation group or 3 cycles of maintenance MVP group.

Response is assessed after the completion of chemotherapy and in one month after the completion of radiotherapy by computerized tomography. A complete response was defined as the disappearance of the tumor by CT scan. A partial response was defined as a reduction of more thaen 50 percent of measurable disease and a minimal response as a reduction of less than 50%.

RESULTS

Until August 1991, 18 patients were registered to this study. The characteristics of the 18 patients are shown in Table 1. Age of the patients ranges from 45 to 75 years with the median of 61. The majority of patients are male. 4 cases were stage IIIa and 14 were stage IIIb. Among 18 cases 2 were lost to follow-up after 2 cycles of chemotherapy, then 16

Table 1. Patient Characteristics (1991.1 – 1991.8)

Characteristics	No. of Patients (%)
Age (years)	
Range	45 – 75
Median	61
Sex	
Male	16 (89)
Female	2 (11)
Stage	
IIIa	4 (22)
IIIb	14 (78)

were analyzed. The response rate of induction chemotherapy was 62.5%; partial response, 50% and minimal response, 12.5% (Table 2).

Residual tumor of the one partial responder was completely disappeared after radiotherapy. 6 cases were progressed during induction chemotherapy and 4 of them were also progressed after radiotherapy (Table 3). All patients were tolerated BID radiotherapy without definite increase of acute complications, compared with conventional radiotherapy group. But at the time of this report one patient expired in two month after the completion of the radiotherapy.

Table 2. Locoregional Response After Neoadjuvant Chemotherapy

	No. of Patients (%)
CR	0/16 (0)
PR	8/16 (50)
MR	2/16 (13)
PD	6/16 (37)

Table 3. Locoregional Response After RT

After CT	After RT
PR (3)	CR (1)
	PR (2)
PD (5)	MR (1)
	PD (4)

High resolution computerized tomograpy and open lung biopsy was taken to clarify the cause of severe dyspnea of this patient. High resolution CT shows a diffuse increase of interstitial marking in whole lung field (Fig. 2). So we took open lung biopsy at the left lower lobe which was far from radiation field. The pathologic specimen showed a severe diffuse interstitial fibrosis compatible with chemotherapy related pulmonary toxicity(Fig. 3).

DISCUSSIONS

Approximately 75% of lung cancer patients have non small cell lung cancer, and two-thirds of

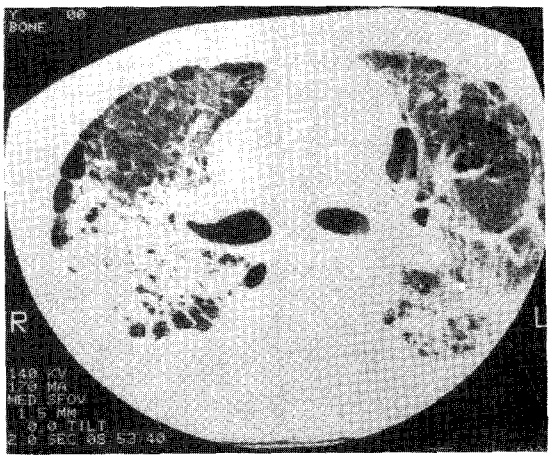

Fig. 2. High Resolution CT: diffuse increase of interstitial marking in whole lung field.

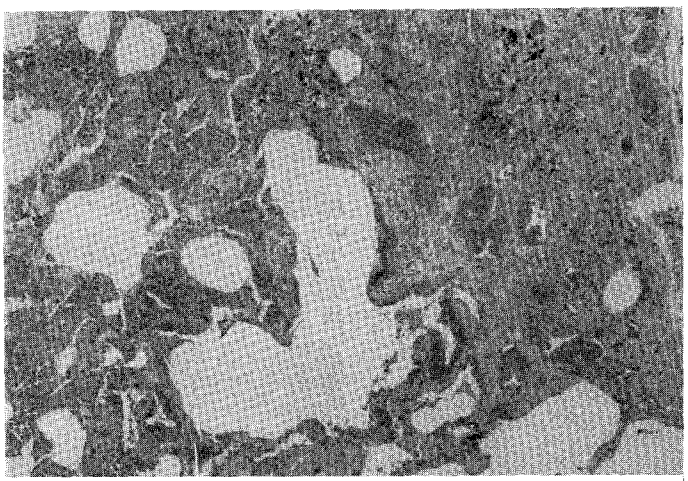

Fig. 3. Severe diffuse interstitial fibrosis compatible with chemotherapy related pulmonary toxicity.

these patients have locally advanced unresectable disease. The median survival for the locally advanced group of patients is reportedly 9-12 months despite efforts to treat them with either surgery[5] and/or radiation therapy[6,7]. Given the presence of micrometastatic disease, effective systemic therapy should have improved survival in advanced non-small cell lung cancer. There are multiple comibination chemotherapy programs currently in use. Particularly cisplatin based programs seem to produce superior response rates. Mitomycin C, vinblastine, and cisplatin combination chemotherapy has produced response rates of 30% to 70%[8,9].

In our study, the response rate of induction chemotherapy was 62.5%; patial response, 50% and mininal response, 12.5%. There are multiple possible ways to combine chemotherapy and radiotherapy, including concomittant administration, sequential administration. For concomittant administration the major advantage is the delivery, without undue delay, of both modalities. The advantage of sequential administration is the avoidance of interaction between the two modalities and reduction of cumulative effects. The disadvantage is the long protraction of the treatment.

In our study, neoadjuvant chemotherapy is used with the intent of increasing the potential for local control by radiotherapy and delivering the earliest possible treatment to micrometastatic disease[10]. In 1984 Cancer and Leukemia Group B initiated a prospective randomized study comparing neoadjuvant chemotherapy followed by radiotherapy to radiotherapy alone in patients with stage III NSCLC. They reported that a median survival was 13.8 months for the CT-RT group and 9.7 months for the RT alone group. ($p=.0022$)[4] To improve the effect of radiotherapy we use hyperfractionated radiotherapy. A phase I/II trial of hyperfractionated radiotherapy for non small cell lung ca was conducted by the Radiation Therapy Oncology Group (RTOG) between 1983 and 1987. Fractions of 1.2 Gy were administered twice daily with more than 4 hours between fractions. Patients were randomized to receive minimum total doses of 60.0, 64.8 and 69.6 Gy. Survival with 69.6 Gy (median, 13 months; 2years, 29%) was significantly ($P=.02$) better than the lower total dose[3]. In consideration of the performance of the Korean people, a total dose of 64.8 Gy was selected. All patients were tolerated hyperfractionated radiotherapy without definite increase of acute complications thus far. So we consider to increase the total dose to 69.6 Gy or higher.

Since there is no significant data about maintenance adjuvant chemotherapy we also study the effect of maintenance MVP chemotherapy by randomization after the completion of the radiotherapy. Although the longer follow up is needed, authours are encouraged with higher response rate and acceptable toxicity of this treatment. We believe that this study is worthwhil to continue.

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= 국문초록 =

제 3 기의 진행성 비소세포 폐암에서의 MVP 복합 항암 용법과 다분할 방사선 치료

— 추가 항암 요법에 대한 임의 선택 —

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제 3 기의 진행성 비소세포 폐암에서의 MVP 항암 요법과 다분할 방사선 치료의 효과를 판정하기 위하여 1991년 1월부터 전향성 임의선택 연구(prospective randomized study)를 시작하였다. 본 연구는 제III기의 비소세포 폐암중 절제가 불가능한 환자를 대상으로 하여 MVP 항암요법 (Mitomycin C 6 mg/m², Vinblastine 6 mg/m², Cisplatin 60 mg/m²)을 3회 시행한 후 다분할 방사선치료 (120 cGy/fx, BID)를 6500 cGy까지 조사하였다. 방사선치료가 끝난 1개월 후 관해정도를 확인하여 추가 항암요법을 시행하는 군과 계속 관찰하는 군으로 임의 분류하였다. 1991년 8월까지 18명의 환자가 등록 되었으며 이중 2명은 2 cycle의 항암요법 후 치료를 포기하여 16명의 환자에 대한 분석을 시행하였다. MVP 항암요법에 대한 관해율은 62.5%로 50%에서는 부분관해 12.5%에서는 minimal response를 보였다. 항암요법에 부분관해를 보인 3명중 1명에서는 방사선 치료후 완전관해를 보였으며 항암요법으로 병이 진행된 6명의 환자중 4명에서는 방사선 치료후에도 역시 병이 진행되는 것을 알 수 있었다. 모든 환자는 다분할 방사선 치료를 잘 견뎠으나 한 환자가 방사선 치료 한달 후 항암요법과 관련된 부작용으로 사망하였다. 아직 추적관찰 기간이 짧고 대상 환자가 많지 않다는 문제점은 있으나 본 연구를 계속 진행함으로써 유의한 결과를 얻을 수 있을 것으로 기대된다.