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Review of the Cases with Squamous Cell Carcinoma of the Lung Treated with Bleomycin, Adriamycin and Radiotherapy.

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INTRODUCTION

Lung cancer is one of the most common malignancies in Japan. In our institution, we observe about 60 cases a year, of which most common histologic type is squamous carcinoma that is about 50% of all lung cancer during the past 7 years. We report our experience with a combination chemotherapy consisting of bleomycin and adriamycin with or without radiotherapy in patients with surgically unresectable squamous carcinoma of the lung.

MATERIALS AND METHODS

Patients with microscopically confirmed squamous carcinoma of the lung between July 1977 and August 1979 were eligible, provided patients were judged inoperable because of the extent of the neoplasm, the presence of metastasis or were found to have nonresectable neoplasm at a time of exploratory thoracotomy. Patients were defined as having limited disease in whom on the basis of clinical measurements, the tumor was confined to the

hemithorax and ipsilateral supraclavicular nodes. All other were defined as having extensive disease.

TABLE-I

Treatment Schedule

ADRIAMYCIN	20mg 2/w 2w (80mg)	20mg 2/w 2w (80mg)
	(2 to 3w rest)	
BLEOMYCIN	15mg 2/w	≒200~300mg
RADIOTHERAPY	2,000red/5days	2,000rad/5days
	(3w rest)	

(for limited disease)

w: week

Regimen used was as follows. If the patient had extensive disease, bleomycin was given in a dose of 15 mg as a i.v. infusion twice weekly until cumulative dose reached 200mg or 300mg, provided severe toxicity such as clinical or roentgenologic evidence of pulmonary fibrosis, a decrease of 10mg or more in PO_2 or a decrease of 5% or more in vital capacity was not observed. Twenty mg of adriamycin was given by i.v. push slowly twice weekly for 2 weeks and was repeated in the same way after a 2 or 3 weeks period if hematologic toxicity was resolved. If the lowest white blood cell count had not recovered to 4,000/mm^3, the platelet count to 50,000/mm^3, clinical evidence of cardiotoxicity or other severe toxicity was found, therapy was delayed. To the patient defined as having limited disease, radiation therapy was instituted. A course of 2,000 rads was given over 5 days and was repeated after a 3 weeks rest period, reaching cumulative doses of 4,000 rads.

As adjuvant therapy, immunostimulant drug such as picibanil or PS-K was given.

Response was defined as 50% or more decrease in sum of the products of any measured lesion. Unchange was defined as either increase or decrease within 50% of lesions in size without appearance of any new lesion. Progression was defined as increase more than 50% in size of measured tumor lesions and or development of new lesions. Karnofsky scale was also employed to assess response.

RESULT

Characteristics of patients at the onset of disease are described in TABLE-II. There were twelve patients on the trial. All were male and their age ranged from 47 to 72 years, that is, 62.5 years in average.

Responses were seen in 5 patients (case 3, 6, 9, 10, 11). Three patients were unchanged and four patients were progressive (TABLE-III). According to Karnofsky scale, improvement was observed in five patients of whom 1 case showed I-B and four cases I-A and

TABLE-II

Clinical Charactaristics and Responses

Patient	Age	sex	Clinical Stage	Total Dose (mg)	Rad	Response	Survival Time (weeks)	X-RAY
1.U.N.	59	M	$T_2N_1M_1$	ADM 160 BLM 105	−	O-A N	15	
2.S.K.	47	M	$T_2N_1M_1$	ADM 80 BLM 110	−	O-B N	19	
3.S.S.	55	M	$T_3N_2M_0$	ADM 260 BLM 195	+	I-B R	51	
4.U.Z.	62	M	$T_3N_1M_0$	ADM 120 BLM 75	−	O-C U	17	
5.T.S.	70	M	$T_3N_1M_0$	ADM 80 BLM 45	+	O-B N	51	
6.K.M.	80	M	$T_3N_2M_1$	ADM 80 BLM 120	−	I-A R	43	
7.O.S.	72	M	$T_3N_1M_0$	ADM 50 BLM 75	−	O-C U	47	
8.M.R.	58	M	T_3N_1M	ADM 80 BLM 65	−	O-C U	7	
9.H.T.	52	M	$T_3N_1M_1$	ADM 60 BLM 45	−	I-A R	60	
10.S.S.	68	M	$T_3N_1M_0$	ADM 220 BLM 90	−	I-A R	26	
11.S.K.	65	M	$T_3N_1M_0$	ADM 140 BLM 165	+	I-A R	13	
12.U.F.	62	M	$T_3N_1M_0$	ADM 80 BLM 90	−	O-O N	26	

ADM; Adriamycin. BLM; Bleomycin. R; Response. U; Unchange.
N; No response. Rad ; Radiotherapy.

TABLE-III Number of patient with Response

Response	Unchange	No response
5	3	4

all other patients except 1 case (O-O) mildly responded either subjectively or objectively (TABLE-IV). The median duration of survival of all patients after initiation of therapy was 35.5 weeks (TABLE-V). Responders among the patients on the trial showed 39 weeks in median survival time (MST), while that of nonresponders was 23 weeks. The median

TABLE-IV Karnofsky Scale

I-C	I-B	I-A	O-C	O-B	O-A	O-O
0	1	4	3	2	1	1

TABLE-V Median Survival Time

All patients	35.5 weeks
Responders	38.6 weeks
Non-responders	23.1 weeks

total doses of adriamycin and bleomycin in the responders were 150mg and 123mg respectively, while the nonresponders were given 93mg of adriamycin and 81mg of bleomycin in their median total doses. Two of three patients who recieved additional radiotherapy responded well.

SIDE EFFECT

Types and frequency of side effect are listed on TABLE-VI. The most frequent side effect was stomatitis and alopecia which were seen in 4 cases, but not serious and were reversible without exceptions. Decrease of WBC below 4,000/mm^3 was seen in 2 cases, but no episode of leukopenic infection developed. Two patients had fever possibly caused by bleomycin. Nausea or epithelitis were minimal. Clinically evident cardiac toxicity and pulmonary fibrosis were not observed.

TABLE-VI SIDE EFFECT

Toxic manifestation	Number
Leukopenia	2
Stomatitis	4
Alopecia	4
Pigmentation	3
Nausea	1
Vomiting	0
Epithelitis	1
Skin rash	1
Fever	2
Cardiotoxicity	0
Pulmonary fibrosis	0

There were no severe toxicities and no deaths which could be attributed directly to adverse reactions of the treatment.

DISCUSSION

Lung cancer is one of the most common malignancies in Japan. However, chemotherapy for the disease has not yet been settled with thorough success. For the spuamous carcinoma of the lung, adriamycin, anthracycline antibiotic drug isolated from culturs of streptomyces peucetius, is known to be effective in its single use. Adriamycin enters the cell rapidly and acts on nuclear structurs with consequent inhibition of mitosis and synthesis of nucleic acid. The concentration of the drug in serum remains fairly stable for seven to ten days.[1] Blum et al.[2] observed a high response rate of 33% against squamous carcinoma of the lung treated with adriamycin alone which is one of the most effective agent.[3,4] Although bleomycin alone has been reported to be active, less than 10% of patients with squamous carcinoma of the lung responded.[5,6] Treatment with bleomvcin is useful generally in combination with other drugs or with radiotherapy.[5,6,7] Bleomycin has been shown to cause scission of single strand DNA and to destroy DNA irreversely when combined with radiotherapy, enhancing killing of tumor cells. Clinically good response against squamous cell carcinoma has been observed in combination with radiotherapy.[8,9,10]

Chan[8] who reported good response rate and prolonged survival time in limited disease, suggested that bleomycin positively enhanced local control of primary disease, but it might be slightly effective in inhibiting the development of systemic metastasis and they recommended additive agents. On the point of combined therapy with other drug, Livingston[11] and konno[12] has recommended combination therapy with vincristine, cytosine arabinoside or endoxan. However, it seems that there is no evidence to conclude that any therapeutic modality has definitely succeeded in chemotherapy of spuamous carcinoma of the lung.

In a point of the above view, we have tried to treat with a combination therapy consisting of bleomycin and adriamycin with or without radiotherapy, expecting their synergistic antitumor effects. Our result showed that 5 of 12 patients achieved response. Overall median survival time was 35.5 weeks. The median survival time of responders was 39 weeks.

In squamous cell cancer which disseminated beyond the hemithorax at its presentation, Green[13] showed increase of the survival time with nitrogen mustards; 26 weeks vs 11 weeks for placebo group. Livingston et al.[14] erported that COMB (cyclophosphomide, oncovin, M-CCNU and bleomycin) therapy showed response rate of 33%, but the median survival time of 9.5 weeks and 12.5 weeks even in responders.

COMB therapy produced a variety of toxic manifestations. Myelosuppression was

marked with 6% of drug-related mortality on this base. The overall incidence of drug-related mortality was 10%. After their experience in COMB therapy, they reported improvement in survival with BACON (bleomycin, adriamycin, CCNU, oncovin and nitrogen mustard).[15] In their study, response rate was 42% and overall median survival time was 20 weeks. The MST of responders and unchanged patients was 26 weeks. Recently, study by Leroy et al.[1] showed the MST of 24.5 weeks on combined chemotherapy with adriamycin plus cyclophosphamide. On BACON therapy, though myelosuppression was not so marked, bleomycin-induced lung damage occurred in 4%, with one fatal case. On comparison with the above mentioned reports by others, response and survival time were better and there were no severe toxicities as such in our method of treatment.

The adverse effects of adriamycin reported are bone marrow suppression, cardiotoxicity, stomatitis, alopecia and gastrointestinal disturbances, etc.[4,16,17] The most important toxicity is bone marrow suppression. However, we observed leukopenia below 4,000/mm^3 in only 2 cases and no severe depression of thrombocyte or red blood cell in our treatment schedule. Because of the duration of the long plasma half life of adriamycin,[1,4] repeated daily administration of the drug is not necessary and intermittent use such as ours would evidently reduce serious adverse reactions with further favourable outcome.

It could be also notable in our study that our method allowed hematologic recovery, and none revealed clinically evident cardiac toxicity, though subclinical one can not be excluded since daily electrocardiogram and cardiac enzyme determinations were not performed unless clinically indicated. It has been reported that clinically evident cardiotoxicity is unusual when the total dose of adriamycin has been restricted to less than 600mg/m^2 [16,17]. Weiss[17] observed that 8 of 149 (5.4%) given adriamycin weekly who have recieved over 600mg/m^2 of the drug were suspected of having an adriamycin-induced cardiomyopathy and one patient died of it. In our group of patients, maximal doses was 260mg in case 3. The absence of clinically evident cardiotoxicity in our group of patients may reflect the restriction of the total administered dose.

The major adverse effect of combined therapy with bleomycin and radiation is pulmonary toxicity. The development of pulmonary toxicity is generally thought to be dose-related, with the incidence rising rapidly above a total dose of 200mg[6] or 450mg[5] of bleomycin, though it has been reported to occur even with low dose.[6,10] Haas[6] described that since all patients ultimately responded had shown at least improvement prior to receiving 200mg in total, doses exceeding this level in nonresponding patients must be indivisualized with regard to potential benefit and toxicity. Chan et al.[8] recommended that the total cumulative dose of bleomycin should be kept below 300mg when this drug is given with external irradiation as combined therapy.

In our study, the median total doses of bleomycin in responders were 123mg (ranging from 45mg to 195mg) and those in nonresponders were 81mg(ranging from 45mg to 110mg). Severe pulmonaly complications caused by bleomycin have not been observed throughout our study in which simultaneous and restricted administration of bleomycin and adriamycin with short course radiotherapy was scheduled. The other toxic manifestations such as stomatitis, alopecia, fever, pigmentation of skin or nail, skin rash, epithelitis and nausea were not serious and were reversible except for pigmentation of nail or skin. Clinical results of combination chemotherapy of bleomycin and adriamycin with or without radiotherapy established by us were obviously effective in treatment of squamous carcinoma of the lung and the treatment was well tolerable to patients.

In order to conclude definitely, however, that our method of treatment in squamous cell carcinoma is exceedingly effective, further evaluation must be done by treating patients in larger scale, and observing longer duration of courses.

SUMMARY

Twelve patients with squamous cell carcinoma of the lung that was judged inoperable were treated with bleomycin and adriamycin. Sequential split course radiotherapy was added when disease was limited to one hemithorax and draining scalene nodes. Five of 12 patients responded (50% or more regression of neoplasm). The median survival time of all patients was 36 weeks. Responders had the median survival time of 39 weeks, while nonresponders had that of 23 weeks. Our regimen was well tolerated to patients, without any serious adverse reaction.

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