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COMBINATION THERAPY WITH BESTATIN IN INOPERABLE LUNG CANCER

A randomized trial

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Abstract

A randomized trial of combination therapy with bestatin (30 mg daily, every day) was performed in 238 patients with inoperable primary lung cancer from August, 1981 through April, 1984. Of the 238 patients, 227 were evaluable: 113 treated by bestatin combination therapy and 114 controls. There was no statistically significant difference in response rate or survival between the 2 groups. In squamous cell cancer response was observed in 34.5% of the bestatin group and 17.9% of the control group. The analysis, including Cox's proportional hazard model, revealed that the survival tended to be longer in the bestatin group (median survival 40 weeks) than in the control group (median survival 24 weeks; $p = 0.051$). This suggests that addition of bestatin might be beneficial in squamous cell cancer of the lung but further, more rigidly controlled, clinical trials are necessary before more definitive conclusions can be drawn.

Key words: Lung cancer, inoperable, bestatin, chemotherapy, randomized trial.

Bestatin (N-[(2S, 3R)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine (commercial name: Ubenimex), is a low molecular synthetic material discovered in the filtrated medium of *Streptomyces olivoreticuli* and detected by Umezawa et al. (1) in 1976, which has been shown to express immunomodulating effects and antineoplastic activity in animal experiments (2). In addition, a clinical phase I study (3) has shown an extremely low toxicity at doses of 30–100 mg daily. In the period from August 1981 to April 1984, we studied the possible effect of bestatin on inoperable primary lung cancer patients when given in addition to chemotherapy or radiotherapy.

Material and Methods

The patients were admitted to the Osaka Prefectural Habikino Hospital with primary lung cancer confirmed histologically or cytologically and judged to be inoperable. Patients under 75 years of age, with an ECOG performance status (PS) from 0 to 3, with no prior treatment, with measurable or evaluable lesion, and with normal bone marrow function (WBC > 4 000/mm^3 and platelet count > 100 000/mm^3) were chosen for the trial. Patients with abnormal hepatic or renal function, with serious pulmonary or cardiac complications, or with active double primary cancers were not included.

The patients were before randomization stratified by histological type (squamous cell cancer, adenocarcinoma, large cell carcinoma, and small cell cancer (SCLC)) and by clinical stage. They were then randomly allocated by the sealed envelope method either to a group which received further bestatin (called the bestatin group) or a control group. For clinical staging of non-small cell lung cancer (NSCLC), the UICC's TNM classification (1981) was followed. SCLC was classified as limited disease (LD) if confined to one hemithorax including the bilateral supraclavicular nodes and as extensive disease (ED) if the tumor was spread outside these limits. Patients in the bestatin group received bestatin (Ubenimex) 30 mg orally per day from the day when they began chemotherapy or

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radiotherapy. The planned period of bestatin administration was more than 60 days and unbroken administration was carried out as far as possible.

Response was evaluated objectively. Complete response (CR) was defined as the disappearance of all evidence of disease for at least four weeks. Partial response (PR) was defined as a $\geqq 50\%$ reduction of the product between the longest perpendicular diameters of the tumors without progression of other lesions and lasting for at least 4 weeks. No change (NC) was defined as any response less than PR, and progressive disease (PD) as a $\geqq 25\%$ increase in lesions or the appearance of new lesions. Survival curves were derived by the method of Kaplan & Meier, and analyzed by the generalized Wilcoxon test. Moreover, the survival was analyzed using Cox's proportional hazard model with inclusion of some prognostic factors.

Results

Patients. In the period from August 1981 to April 1984 there were 120 patients allocated to the bestatin group and 118 to the control group. Of these patients 1 had no cancer, 1 had a secondary lung tumor, 1 had performance status 4 at the time of registration and 2 were over 75 years of age, making a total of 5 patients ineligible. In addition, 1 patient had surgical excision performed after registration, 2 refused treatment, and 3 violated the protocol. Thus, 227 patients (113 in the bestatin group and 114 in the control group) were evaluable for response and survival.

The background factors of the 227 evaluable patients are shown in Table 1. A larger number of elderly patients was found in the control group, which had an average age of 64.2 years compared to 60.9 years in the bestatin group ($p < 0.05$). However, no significant difference was found between the 2 groups concerning sex, PS, histological type, or clinical stage. According to the analyses by Cox's comparative hazard model the hazard ratio of PS 2 and PS 3 (instant death rate) was approximately the same, and no association was found between survival and age, which leads to the conclusion that the two groups were reasonably well comparable. No significant differences in background factors (sex, age, PS, clinical stage) between the two groups were found in the patients with squamous cell cancer (Table 2).

Basic treatment. Various regimens were used as basic antineoplastic treatment (Table 3). The patients with squamous cell cancer were treated with radiotherapy+ tegafur, doxorubicin (DOX) containing, cisplatin (CDDP) containing, or other regimens. The patients with adenocarcinoma and large cell carcinoma received courses containing either DOX or CDDP. Among the patients with SCLC some received a 4-drug combination regimen (CONP) of cyclophosphamide + vincristine + nidran + procarbazine, some received CONP alterating with VAD (etopside+

Table 1

Background factors of all cases in which evaluation was possible

	Bestatin (n = 113)	Control (n = 114)	p-value
Sex			
Male	92	87	NS
Female	21	27	
Age			
–49	12	8	
50–59	33	17	$p < 0.05$
60–69	46	55	
70–	22	34	
Mean ± SD	60.9 ± 9.6	64.2 ± 7.6	$p < 0.05$
Histology			
Sq.	38	36	
Ad. + Lar.	40	41	NS
Sm.	35	37	
Stage			
I	2	3	
II	4	3	NS
III	59	61	
IV	48	47	
PS			
0	6	3	
1	60	59	$p < 0.1$
2	34	25	
3	13	27	

Sq. = squamous cell cancer.
Ad. = adenocarcinoma.
Lar. = Large cell cancer.
Sm. = Small cell cancer.

Table 2

Background factors in squamous cell cancer patients

	Bestatin (n = 38)	Control (n = 36)	Significance
Sex			
Male	33	32	NS
Female	5	4	
Age			
–49	0	2	
50–59	7	2	NS
60–69	18	17	
70–	13	15	
Mean ± SD	65.3 ± 7.0	66.6 ± 6.9	NS
Stage			
I	2	2	
II	3	3	NS
III	23	22	
IV	10	9	
PS			
0	2	0	
1	20	18	NS
2	12	9	
3	4	9	

Table 3

Histological type and treatment

Treatment	Bestatin	Control	Significance
Squamous cell ca.			
RT + tegafur	16	11	
Containing DOX	7	7	NS
Containing CDDP	4	6	
Others	11	11	
Adenoca. + large cell ca.			
Containing DOX	13	10	
Containing CDDP	9	14	NS
Others	18	17	
SCLC			
CONP-VAD	18	21	
CONP	13	14	NS
COAP	4	2	

RT = radiotherapy, DOX = doxorubicin, CDDP: cisplatin.
CONP = cyclophosphamide + vincristine + ACNU + procarbazine.
COAP = cyclophosphamide + vincristine + DOX + procarbazine.
VAD = etoposide + doxorubicin + cisplatin.

DOX + CDDP) (alternating non-cross resistant chemotherapy (4)), while other patients received COAP (cyclophosphamide, vincristine, doxorubicin, procarbazine). No essential difference was observed in the basic therapeutic regimens between the bestatin group and the control group.

Response. There were 93 patients in the bestatin group and 86 in the control group in whom the response could be evaluated (Table 4). Concerning squamous cell cancer the response rate was 34.5% (10/29) in the bestatin group and 17.9% (5/28) in the control group but the difference was not statistically significant. The response rate for adenocarcinoma and large cell carcinoma taken together was 6.7% (2/30) in the bestatin group and 7.4% (2/27) in the control group. The response rate for SCLC was 64.7% (22/34) in the bestatin group and 87.7% (21/31) in the control group and the difference was not significant.

Survival. The survival was analyzed in May 1989, when

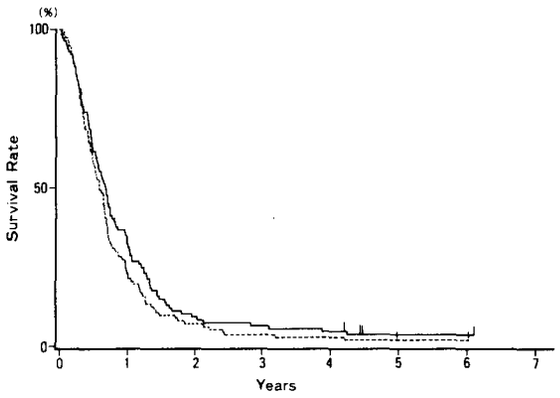

Fig. 1. Survival curves of all eligible patients (NS; $p = 0.25$). —— Bestatin ($n = 113$); median survival 8.1 months. - - - Control ($n = 114$); median survival 7.0 months.

the minimum follow-up period was 4 years. In the survival curves for all patients (Fig. 1), no difference was seen between the two groups ($p = 0.25$). The median survival was 247 days in the bestatin group and 212 days in the control group. When survival curves were adjusted for stage, PS, and histological type, i.e. factors most strongly associated with survival according to analysis with Cox's hazard model, the hazard ratio was 0.87 in the bestatin group compared to 1 in the control group and no significant difference was seen between the two groups ($p = 0.32$).

When the squamous cell cancers were analyzed separately, there was significantly longer survival in the bestatin group than in the control group ($p < 0.05$) (Fig. 2). The median survival in the bestatin group was 278 days and in the control group 166 days. With survival analyzed with the proportional hazard model, and the control group given hazard ratio of 1, the hazard ratio for the bestatin group was 0.60, and $p = 0.051$.

In the patients with adenocarcinoma or large cell carcinoma (Fig. 3) and with SCLC (Fig. 4), no differences in

Table 4

Tumor response

Histology group	Eligible cases	Response					Significance
		CR	PR	NC	PD	Rate (%)	
Squamous cell ca.							
Bestatin	29	0	10	16	3	34.5	NS
Control	28	0	5	19	4	17.9	
Adenoca. + large cell ca.							
Bestatin	30	0	2	23	5	6.7	NS
Control	27	0	2	22	3	7.4	
SCLC							
Bestatin	34	4	18	11	1	64.7	NS
Control	31	6	15	8	2	67.7	

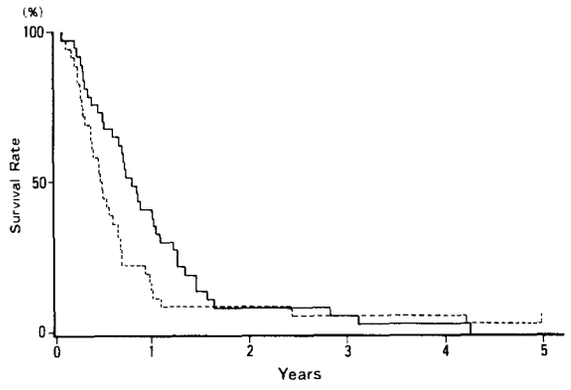

Fig. 2. Survival curves of squamous cell carcinoma cases ($p < 0.05$). —— Bestatin ($n = 38$); median survival 9.1 months. – – – Control ($n = 36$); median survival 5.5 months.

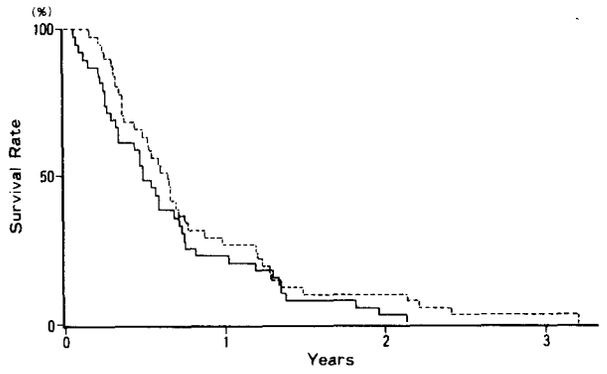

Fig. 3. Survival curves of adenocarcinoma and large cell carcinoma cases (NS). —— Bestatin ($n = 40$); median survival 5.6 months. – – – Control ($n = 41$); median survival 7.6 months.

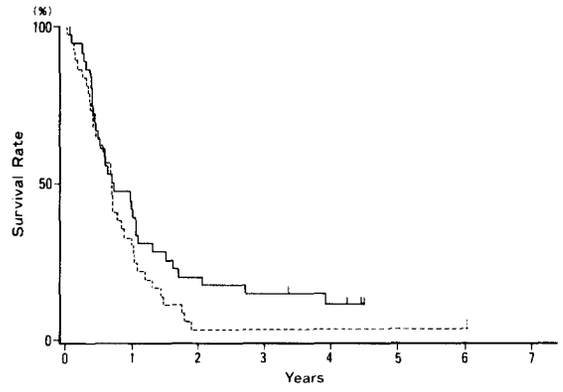

Fig. 4. Survival curves of small cell carcinoma cases (NS). —— Bestatin ($n = 35$). – – – Control ($n = 37$).

the survival curves between the two arms were recognized. Median survival for the patients with adenocarcinoma or large cell carcinoma was 170 days for the bestatin group and 232 days for the control group. The corresponding median survival times for SCLC were 257 and 258 days respectively.

Side-effects. Due to the diversity of the basic treatment regimens, a comparison of side-effects between the two groups was not possible. However, no side-effects or abnormal test values thought to be attributable to bestatin were observed.

Discussion

Bestatin is a biological response modifier (BRM), classified as belonging to the immunomodulator and/or immunostimulator category. It exerts in vivo effects on macrophages, T-cells, and NK cells, etc., and the tumor shows regression, which is sometimes caused by bestatin, can probably be regarded as a strengthened immune effect (5).

Several clinical studies with bestatin have been reported. Ota el al. (6) performed a randomized study of patients with acute non-lymphocytic leukemia who were in complete remission, and found significantly prolonged survival in the bestatin group. Ikeda et al. (7) conducted a randomized study in patients with stage Ib and stage II malignant melanoma receiving radiotherapy and reported a significant prolongation of survival and disease-free survival in the bestatin group.

No difference in survival between the control group and the bestatin group was seen in our study when all patients were included. However, among the squamous cell cancer patients a longer survival was found in the bestatin group ($p = 0.014$). Yasumitsu et al. (8), in a randomized trial with patients with resected lung cancer, also reported that bestatin prolonged the survival in patients with squamous cell cancer.

These clinical results suggest that bestatin might be useful in lung cancer, especially squamous cell carcinoma, but the results obtained are not conclusive, because there are too few patients and the basic treatments lack uniformity. To evaluate BRMs, such as bestatin, which do not have a direct antineoplastic activity, a prospective randomized trial is necessary with the patients stratified according to the major prognostic factors and treatment methods. Also, the most effective combination regimens should be used as basic treatment. To attain statistical significance, a large number of patients should be entered in such a study.

Based on these considerations, we have started a cooperative randomized trial with bestatin in patients with stage IIIA, IIIB and IV squamous cell lung cancer using the double blind method and with a combination of CDDP and vindesine as basic treatment. It is hoped that the efficacy of bestatin in squamous cell lung cancer will be clarified through this trial.

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