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Abstract

Idiopathic interstitial pneumonia (IIP) is a progressive and often fatal pulmonary disorder, and evaluating the prognosis of patients with IIP has never been sufficient. Accordingly, factors including clinical features, laboratory data, cellular components in bronchoalveolar lavage (BAL) fluid and response to corticosteroid therapy were analyzed in 35 patients with IIP whose median age of respiratory onset was 60 years (range; 37-77 years). Nineteen patients (54.3%) were in the active stage of IIP and 16 of them were treated with corticosteroids. Significant prognostic factors were the neutrophil percentage in BAL fluid, interstitial shadows on chest radiograph, pulmonary function, blood oxygen level, grade of dyspnea, and disease activity at the initial examination. Patients in the active stage showed higher proportions of neutrophils and eosinophils in BAL fluid than those in the non-active stage. Despite corticosteroid therapy, the survival of patients in the active stage was significantly shorter than those in the non-active stage. Fifty percent of the patients treated with corticosteroids were regarded as responders at 1 month after the initiation of therapy; however, there was no significant difference between responders and non-responders in terms of survival time. In conclusion, disease activity and neutrophils in BAL fluid may be important predictors of the prognosis of IIP.

KEYWORDS: idiopathic interstitial pneumonia (LLP), prognostic factor, corticosteroid therapy, bronchoalveolar lavage(BAL), disease activity

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Factors Affecting Prognosis of Idiopathic Interstitial Pneumonia

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Idiopathic interstitial pneumonia (IIP) is a progressive and often fatal pulmonary disorder, and evaluating the prognosis of patients with IIP has never been sufficient. Accordingly, factors including clinical features, laboratory data, cellular components in bronchoalveolar lavage (BAL) fluid and response to corticosteroid therapy were analyzed in 35 patients with IIP whose median age of respiratory onset was 60 years (range; 37-77 years). Nineteen patients (54.3%) were in the active stage of IIP and 16 of them were treated with corticosteroids. Significant prognostic factors were the neutrophil percentage in BAL fluid, interstitial shadows on chest radiograph, pulmonary function, blood oxygen level, grade of dyspnea, and disease activity at the initial examination. Patients in the active stage showed higher proportions of neutrophils and eosinophils in BAL fluid than those in the non-active stage. Despite corticosteroid therapy, the survival of patients in the active stage was significantly shorter than those in the non-active stage. Fifty percent of the patients treated with corticosteroids were regarded as responders at 1 month after the initiation of therapy; however, there was no significant difference between responders and non-responders in terms of survival time. In conclusion, disease activity and neutrophils in BAL fluid may be important predictors of the prognosis of IIP.

Key words: idiopathic interstitial pneumonia (IIP), prognostic factor, corticosteroid therapy, bronchoalveolar lavage (BAL), disease activity

Idiopathic interstitial pneumonia (IIP), histologically documented as usual interstitial pneumonia (UIP) or desquamative interstitial pneumonia (DIP) (1-3) has been extensively studied because of the progressive features of the disease, in which there are hypoxia and diminishing lung volume, followed by fatal respiratory failure. The etiology of IIP is not well established, although an immunological mechanism has been discussed based on the presence of immune complex in the lung tissue (4, 5). The pathogenesis of the fibrosing process in various interstitial lung diseases, including IIP, has not yet been clearly elucidated. Patients with IIP show variable survival times. The patients reported by Hamman and Rich (6) died within 1 year from the onset of respiratory symptoms, whereas survival times reported in other studies ranged from a few months to more than 10 years with or without therapy (7-9). Acute exacerbation of IIP usually causes respiratory failure, this being the primary cause of death. Treatment of IIP with corticosteroids has been unsuccessful; only a small proportion of patients treated with corticosteroids has been reported to show some relief or to recover from the respiratory failure (7-11). Moreover, long-term treatment with high-dose corticosteroids is frequently associated with serious adverse effects. In the present study, we analyzed prognostic factors in IIP in terms of clinical features, laboratory data, bronchoalveolar lavage (BAL) fluid and response to corticosteroid therapy.

Patients and Methods

The subjects were 35 patients with IIP (10 women and 25 men) hospitalized at our institution between 1976 and 1994. The diagnosis of IIP was based on the criteria proposed by the study group of IIP in Japan (12). These criteria include symptoms, physical and laboratory findings, pulmonary function, chest radiographic findings, and lung histology. Lung specimens for the histological

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confirmation of IIP were obtained by transbronchial lung biopsy in 26 patients, by open lung biopsy in 1 patient and at autopsy in 3 patients. None of the patients had any connective tissue diseases throughout the clinical course. The median age of respiratory onset was 60 years (range; 37-77 years). Twenty-one patients (60%) were current smokers or ex-smokers.

Bronchoalveolar lavage (BAL). BAL was performed in 29 patients (82.9%) before they received treatment for IIP and in 29 healthy volunteers (2 women and 27 men, median age was 26 years) as controls. Informed consent was obtained from patients receiving BAL. Following premedication and local anesthesia with 4% lidocaine, the bronchoscope (Olympus TI-10) was wedged in a segment of the middle lobe (B^4 or B^5). Sterile physiological saline was infused in 50-ml each through the bronchofiberscope and immediately aspirated by suction four times (total, 200 ml). The volume of recovered BAL fluid was measured and centrifuged (at 4°C, 250 × *g*, 10 min) to separate the cellular components. The cell pellets were then resuspended in 10 ml of physiological saline and the total number of cells was counted. Differential cell counts of 1000 cells in BAL fluid were done with May-Giemsa staining, in which macrophages, lymphocytes, neutrophils, eosinophils, and basophils were identified.

Gallium scintigraphy (^{67}Ga). Gallium citrate (3mCi) was given intravenously and gallium uptake by lungs was examined with a whole body scanner 48 h later. The ^{67}Ga uptake in the lung fields was assessed as negative or positive by radiologists (4, 13, 18).

Evaluation of chest radiographic findings. Interstitial shadows on chest radiographs were classified into four types: type I, granular with frosted-glass like shadow; type II, reticulonodular shadow; type III, honeycombed shadow with multiple small and large rings; type IV, diaphragmatic elevation reflecting lung volume loss. Type III and IV shadows indicate overt fibrosis in the lungs.

Assessment of dyspnea. The degree of dyspnea on exertion was graded according to the Hugh-Jones classification (I-V): I, average activity is possible such as walking on the level and going up stairs; II, walking on the level is possible similar to others, but going up hills or stairs at normal pace is impossible; III, even walking on the level at normal pace is impossible, but walking at own pace on the level is possible; IV, without taking a rest, walking more than 50 m is impossible; V, dyspnea occurs at rest or slight exertion (14).

Pulmonary function tests and blood gas analysis. Total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in one second ($FEV_{1.0}$), $FEV_{1.0}$/FVC ratio ($FEV_{1.0}$%), and diffusing capacity for carbon monoxide (DL_{CO}) were routinely measured by whole-body plethysmography and expressed as a percentage of predicted values. Partial arterial blood gas pressure (PaO_2 $PaCO_2$) in room air was also measured. Complete blood cell counts and blood biochemistry were performed in all patients periodically.

Evaluation of disease activity. The disease activity of IIP was evaluated by assessing changes in symptoms (Hugh-Jones classification), interstitial shadows, and respiratory function (FVC) within the previous 3 months on admission. Exacerbation of more than two of these parameters was regarded as the active stage while no change or exacerbation of one parameter was regarded as non-active.

Analysis of prognostic factors in IIP. Various factors such as age, sex, smoking history, gallium scintigraphy, interstitial shadows, pulmonary function, blood oxygen level, cellular components in BAL fluid, disease activity, and response to corticosteroid therapy were analyzed statistically in relation to the prognosis of IIP.

Assessment of response to corticosteroid therapy. The response to corticosteroid therapy was based on three parameters: grade of dyspnea, change of more than one grade by the Hugh-Jones classification; PaO_2 levels more than 10 Torr of the initial value, and FVC (%predicted) more than 15% of the initial value. When more than one parameter was improved, the therapy was considered to be effective and such patients were regarded as responders.

Statistical analysis. Laboratory data are expressed as means ± SD, and were evaluated statistically with Student's *t*-test. Survival curves were constructed according to the Kaplan-Meier method (15) and statistical analysis was performed with Wilcoxon's test. Survival time from the respiratory onset, BAL procedure, and the initiation of steroid therapy was calculated in relation to various prognostic factors. The significance limit was assessed at the 5% level.

Results

Clinical Features

All patients with IIP had dry cough. On auscultation of the lung, crepitant rales were audible in 32 of the 35 patients. At initial presentation, dyspnea on exertion ranged from grades I to V. Four patients showed no dyspnea. Twenty patients (57.1 %) had dyspnea of grade III or IV. Symptom duration before therapy was 12.9 ± 13.2 months. The median survival time (MST) and the 5-year survival rate of all patients from the onset of respiratory symptoms were 7.1 years and 63.0 %, respectively. Twenty-four patients (68.6 %) died during the follow-up period; 21 of whom (60 %) died of respiratory failure due to exacerbation of IIP, while of the remaining 3, 2 died of lung cancer and 1 died of adenocarcinoma of unknown origin. Of the 29 patients (82.9 %) studied with ^{67}Ga, 21 patients showed positive ^{67}Ga uptake and 8 patients were negative.

Interstitial shadows on chest radiographs were classified as above: 34 patients (97.1 %) had type I, 31 (88.6 %) had type II, 21 (60.0 %) had type III and 26 (74.3 %) had type IV. Nine patients (25.7 %) showed only granular or reticulonodular shadow (type I or II) and 26 (74.3 %) showed honeycombed shadow or diaphragmatic elevation (type III or IV). Pulmonary function tests in most patients revealed decreased vital capacity, low diffusion capacity, and hypoxia (Table 1).

Disease activity was evaluated in all patients based on the criteria described above. Patients in the active stage showed a slightly higher grade of dyspnea, lower PaO_2, lower DL_{CO} (% predicted), and more extensive interstitial shadows than those in the non-active stage. The FVC (% predicted) of patients in the active stage was significantly lower than that of the patients in the non-active stage ($P < 0.01$).

Serum lactate dehydrogenase (sLDH; normal range, 203–442 IU/L) was elevated in 11 patients (31.4 %), all of whom were in the active stage.

Bronchoalveolar Lavage

The mean recovery rate of BAL fluid in IIP was lower and the total cell counts were higher than the values in the normal controls ($P < 0.01$). In the BAL fluid of IIP, the proportions of lymphocytes, neutrophils, eosinophils, and basophils were increased, with a relative decrease of macrophages (Table 2). The proportions of neutrophils and eosinophils were significantly higher in patients in the active stage than in patients in the non-active stage ($P < 0.05$). There were no significant differences in the proportions of macrophages, lymphocytes, and basophils in relation to disease activity (Fig. 1).

Response to Corticosteroid Therapy

The indications for corticosteroid therapy for each patient were determined on the basis of disease activity. Sixteen (45.7 %) of the 35 patients with IIP in the active stage received prednisolone at a dose of 1–1.5 mg/kg/day (not exceeding 100 mg/day) for 1 month, tapered thereafter at 5 mg per month. The 5-year survival rate from respiratory onset in the patients who received steroid

Table 1 Laboratory findings in patients with IIP

Pulmonary function	
TLC (% predicted)	62.0 ± 19.9
FVC (% predicted)	62.3 ± 19.6
$FEV_{1.0}$ %	87.0 ± 11.5
DL_{CO} (% predicted)	42.3 ± 19.1
Blood gas pressure	
PaO_2 (Torr)	70.2 ± 16.8
$PaCO_2$ (Torr)	39.5 ± 5.4
Biochemical findings	
sLDH (IU/L)	421.6 ± 142.5

Values are expressed as means ± SD.
IIP = idiopathic interstitial pneumonia; TLC = total lung capacity; FVC = forced vital capacity; $FEV_{1.0}$ % = forced expiratory volume in one second/FVC ratio (%); DL_{CO} = diffusing capacity for carbon monoxide; sLDH = serum lactate dehydrogenase.

Table 2 Cellular components in BAL fluid of patients with IIP

	Number of patients	Recovery rate (%)	Total cell count ($\times 10^6$)	Differential cell count (%)				
				Mac	Ly	Nt	Eo	Ba
IIP	29	54.5 ± 12.3	25.2 ± 19.7**	73.1 ± 20.5	19.4 ± 17.0	4.7 ± 5.2*	2.8 ± 3.2*	0.3 ± 0.6
Healthy volunteers	29	66.2 ± 13.0	13.9 ± 7.6**	87.7 ± 7.9	11.3 ± 7.8	0.7 ± 0.9*	0.3 ± 0.4*	0.01 ± 0.01

BAL = Bronchoalveolar lavage; Mac = Macrophages; Ly = Lymphocytes; Nt = Neutrophils; IIP = Idiopathic interstitial pneumonia; Eo = Eosinophils; Ba = Basophils. *$P < 0.05$; **$P < 0.01$.

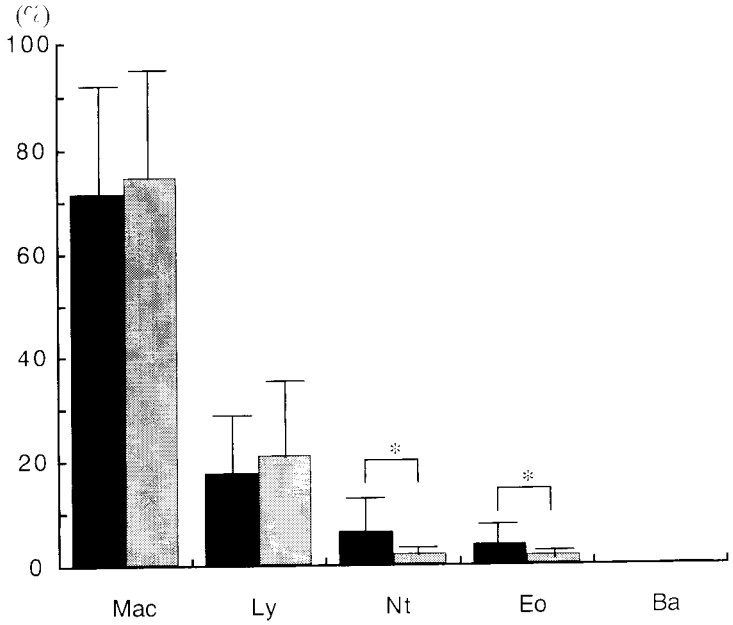

Fig. 1 Comparison of cellular components in bronchoalveolar lavage (BAL) fluid of patients with idiopathic interstitial pneumonia (IIP) in the active and non-active stages. Mac: Macrophages; Ly: Lymphocytes; Nt: Neutrophils; Eo: Eosinophils; and Ba: Basophils. Proportions of neutrophils and eosinophils in the BAL fluid of patients with IIP in the active stage were significantly higher than those in patients in the non-active stage ($P < 0.05$). (■) active; (▒) non-active.

Table 3 Comparison of clinical and laboratory data in relation to therapeutic effects at 1 month

	Responders	Non-responders	*P* value
Number of patients	8	8	
Age at onset (years)	52.6±7.6	59.4±7.6	ns
Sex (men/women)	6/2	5/3	ns
Disease duration (months)	7.5±8.6	16.3±16.0	ns
Lung function			
FVC (%predicted)	44.3±8.5	58.0±15.4	P < 0.05
DL_{CO} (%predicted)	25.5±8.0	46.8±21.0	P < 0.05
Blood gas pressure			
PaO_2 (Torr)	66.4±15.0	70.5±17.0	ns
$PaCO_2$ (Torr)	39.8±8.1	39.3±6.0	ns
sLDH (IU/L)	391.0±70.1	515.1±217.6	ns
BAL fluid			
Total cell count ($\times 10^6$)	42.5±27.4	17.2±9.1	ns
Differential cell count (%)			
Macrophages	77.4±18.5	69.4±22.4	ns
Lymphocytes	12.6±12.9	22.8±18.2	ns
Neutrophils	5.1±5.7	6.2±7.4	ns
Eosinophils	4.6±4.3	1.4±1.3	ns
Basophils	0.3±0.5	0.3±0.7	ns

Values are expressed as means ± SD. ns: not significant; Other abbreviations: See Tables 1 and 2.

therapy was 52.8 %, while the rate was 77.4 % in untreated patients. Six patients required high-dose methylprednisolone therapy intravenously (1000 mg/body/day for first 3 days) because of severe symptoms and pred-

nisolone was administered orally. Steroid therapy improved the symptoms, the respiratory function, and the radiographic findings in some patients at 1 month, 3 months, and 6 months after, respectively. Four patients (25 %) died within 6 months after the initiation of steroid therapy. Only one patient showed improvement in all three parameters during the follow-up period. Eight patients (50 %) responded to steroid therapy at 1 month, six (37.5 %) at 3 months, and three (18.8 %) at 6 months. Three of the six patients who received high-dose methylprednisolone therapy were responders at 1 month and the remaining three died within 6 months. The proportion of responders decreased gradually with the exacerbation of IIP.

Various factors such as age, sex, cellular components in BAL fluid, and other laboratory data before therapy were compared between responders and non-responders at 1 month (Table 3). The values for FVC and DL_{CO} (% predicted) were lower in responders than in non-responders. Age, disease duration, and sLDH were slightly lower in responders. There was no significant difference in the cellular components of BAL fluid between responders and non-responders. At 3 or 6 months of therapy, however, there were no significant differences between responders and non-responders in any factors.

Analysis of Prognostic Factors

Age, sex, smoking. There was no significant difference in survival from onset between younger ($<$ 60 years) and older patients ($>$ 60 years), between men and women and between smokers (ex-smokers and current smokers) and non-smokers.

BAL. Cellular components in BAL fluid were analyzed in relation to prognosis. The patients were divided into two groups according to the proportions of these components in BAL fluid, *i.e.*, those in whom neutrophils were more and less than 5 %, lymphocytes were more and less than 15 %, and eosinophils were more and less than 3 % from the mean values, tentatively. The survival of patients with more than 5 % neutrophils was significantly shorter from the time of the BAL procedure than in those with less than 5 % ($P < 0.01$). The MST in patients with more than 5 % neutrophils was 10.6 months, while the MST in those with less than 5 % neutrophils was 73.0 months (Fig. 2A). All patients with more than 5 % neutrophils died during the follow-up period. There were no significant differences in survival in relation to the proportions of lymphocytes or eosinophils (Fig. 2B, 2C).

Gallium scintigraphy. Twenty-nine patients (82.9 %) were examined with ^{67}Ga. Although there was no significant difference in survival between patients with negative and positive ^{67}Ga, patients with negative ^{67}Ga survived longer; the MST was 38.7 months in patients with positive ^{67}Ga and 80.0 months in those with negative ^{67}Ga.

Interstitial shadows on chest radiographs. There was a significant difference in survival in relation to the type of interstitial shadows. The 5-year survival rate of patients with only type I or II was longer (75.0 %) than those with type III or IV (51.9 %) ($P < 0.05$).

Pulmonary function tests. Patients were divided into two groups according to FVC and DL_{CO} (% predicted) values. Patients with FVC of more than 60 % and DL_{CO} of more than 50 % showed significantly longer survival than those with values of less than 60 % and less than 50 %, respectively ($P < 0.01$, $P < 0.05$). The 5-year survival rate of patients with FVC of more than 60 % was 76.0 %, while that for patients with values less than 60 % was 32.7 %. The 5-year survival rate of patients with DL_{CO} of more than 50 % was 71.4 %, while that for patients with values less than 50 % was 46.9 %.

Arterial blood gas. The patients were divided into two groups according to PaO_2 levels in room air. The 5-year survival rate of patients with PaO_2 level of more than 80 Torr was significantly longer (87.5 %) than those with values of less than 80 Torr (36.3 %) ($P < 0.01$).

Dyspnea on exertion. The 5-year survival rate of patients with mild dyspnea (grade I or II) was significantly longer (81.8 %) than those with severe dyspnea (grade III, IV or V) (50 %) ($P < 0.01$).

Disease activity. Patients in the active stage showed significantly shorter survival than those in the non-active stage ($P < 0.01$) (Fig. 3), the 5-year survival rate from initial examination being 40.9 % in patients in the active stage, compared to 77.1 % in those in the non-active stage.

Response to corticosteroid therapy. There was no significant difference in survival between responders and non-responders at 1 month (Fig. 4), 3 months, or 6 months. The MST at 1 month was 33.0 months in responders, while it was 23.2 months in non-responders. The MST of responders at 3 and 6 months were slightly longer than those of non-responders.

Serum LDH. Patients were divided into two

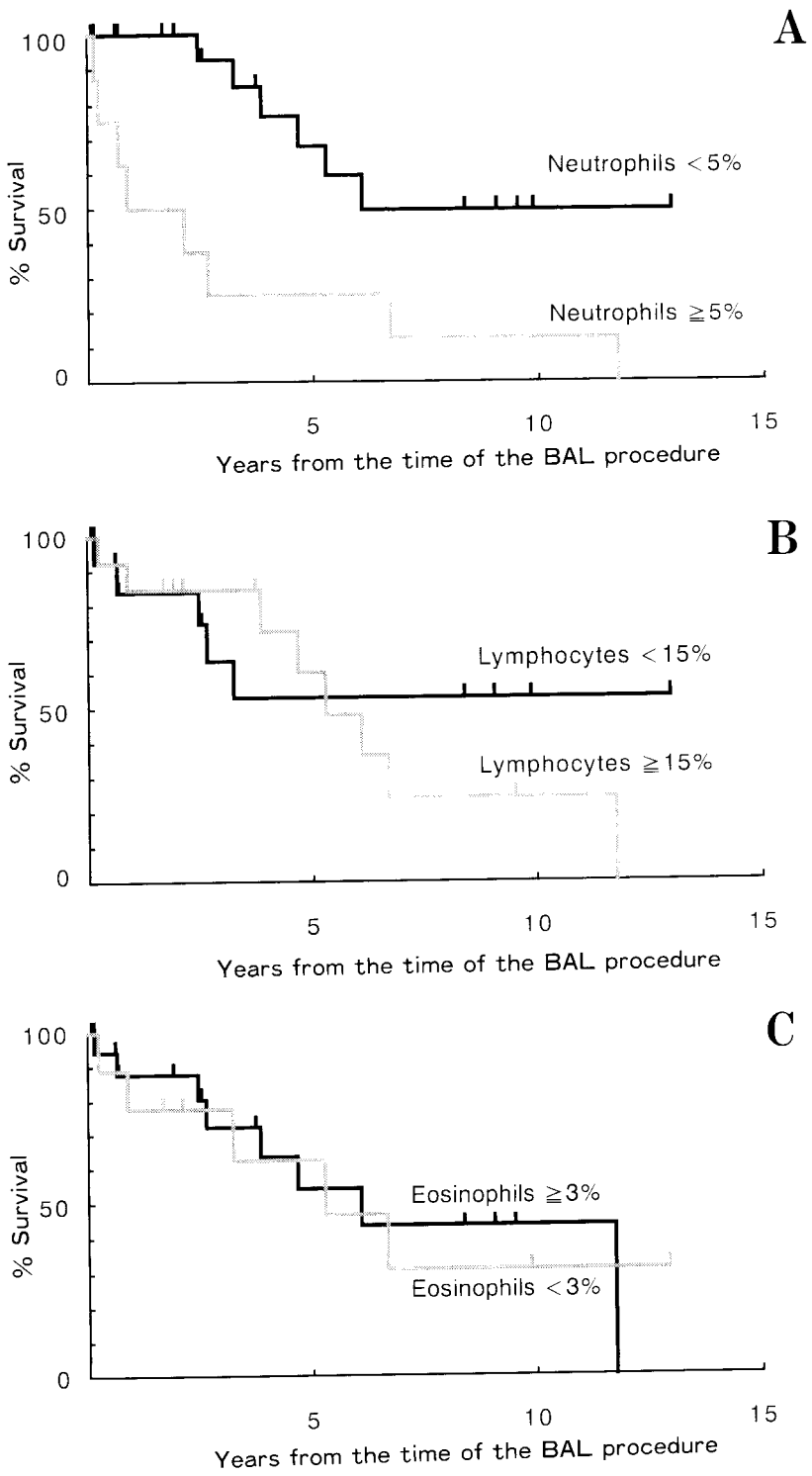

Fig. 2 Survival curves of 29 patients with IIP in relation to cellular components in BAL fluid, **A**: the survival of patients with more than 5% neutrophils was significantly shorter than those with less than 5% ($P < 0.01$). IIP, BAL: See Fig. 1.
There was no significant difference in survival in relation to the proportions of lymphocytes (**B**) and eosinophils (**C**).

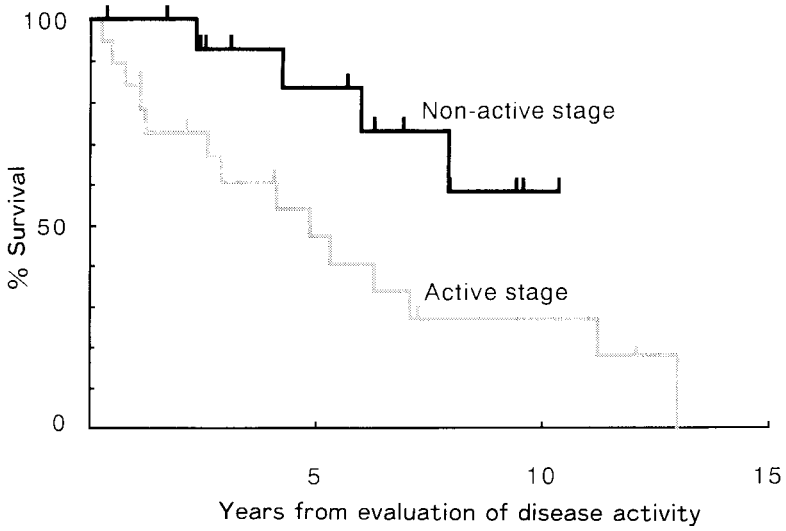

Fig. 3 Survival curves of 35 patients with IIP in relation to disease activity. The survival of patients in the active stage was significantly shorter than those in the non-active stage ($P < 0.01$). IIP: See Fig. 1.

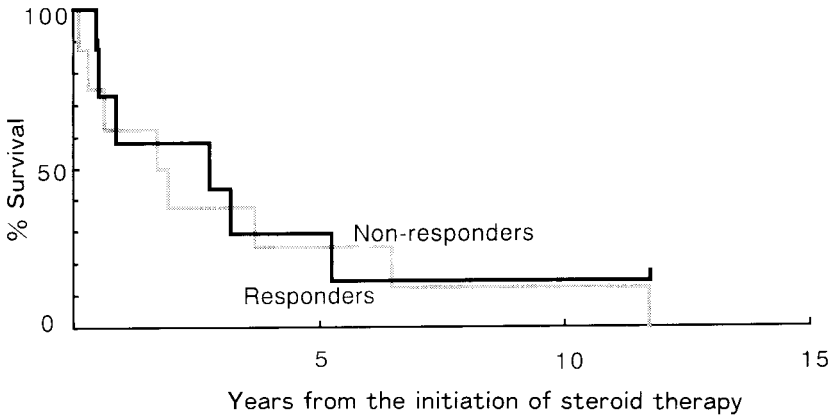

Fig. 4 Survival curves of patients with IIP in relation to response to corticosteroid therapy at 1 month. There was no significant difference in survival between responders and non-reskonders. IIP: See Fig. 1.

groups according to levels of sLDH. Although there was no significant difference in survival between patients with high sLDH and those showing normal levels, patients with normal sLDH did show longer survival. The MST of patients with normal sLDH was 80.0 months, whereas the MST of those with high sLDH was 32.3 months. Further, decreases in sLDH levels of more than 20 IU/L within 1 month after the initiation of steroid therapy were shown in 9 patients (56.3 %) and these patients showed slightly longer survival than those with elevated sLDH who did not show a decrease.

Discussion

IIP is considered to be one of the most serious interstitial lung diseases; spontaneous remission has rarely been observed and the outcome is usually fatal (16-18). Patients with IIP have been shown to have UIP or DIP

histologically and their clinical courses have been classified into chronic and acute form depending on their clinical course (12). All of patients in this study had chronic IIP which was considered to be almost synonymous with the entity described as idiopathic pulmonary fibrosis (IPF) in the United States and cryptogenic fibrosing alveolitis (CFA) in the United Kingdom. In our study, 30 patients (85.7 %) were confirmed as showing UIP histologically. It has been reported that most patients with IPF are treated with corticosteroids, although the effects of such therapy are not regarded as sufficient in terms of achieving objective improvement (7-11). The use of lung transplantation as curative therapy for IPF or CFA has been increasing rapidly in Europe and North America since the 1980s and the postoperative outcome has gradually been improving (19, 20). In the near future, lung transplantation will be carried out in Japan, and the criteria for lung transplantation in IIP in Japan is controversial. Therefore, the evaluation of prognostic factors in IIP is important and urgent. In this study, poor prognosis was shown in patients who had increased interstitial shadows, poor pulmonary function, low PaO_2, and a high grade of dyspnea, while prognosis was not affected by such factors as age, sex, smoking history, gallium scintigraphy, and sLDH. Schwartz *et al.* (21, 22) suggested that poor prognostic factors in IPF included male gender, advanced disease condition with restrictive lung function, abnormal gas exchange, and increased interstitial abnormalities on chest radiographs. Furthermore, they stressed the assessment of dyspnea in patients with IPF as being a particularly important prognostic factor, since patients with moderate to severe dyspnea were found to have an accelerated decline in both lung volume and gas exchange values. In our study, patients with a normal range of sLDH showed longer survival than those with high sLDH and, further, patients whose sLDH levels decreased by more than 20 IU/L within 1 month of therapy showed slightly longer survival. Moreover, sLDH of patients in the active stage was 457.7 ± 170 IU/L and that in the non-active stage was 381.0 ± 92.7. Although sLDH increases in various diseases, monitoring of sLDH levels in the course of IIP could be a good parameter for reflecting disease activity and prognosis. In regard to disease activity, patients with IIP in the active stage showed significantly poorer prognosis than those in the non-active stage. Thus, some patients assessed as being in the active stage could be good candidates for lung transplantation.

BAL is used for the analysis of increased or accumulated cellular components in the lungs of patients with various types of interstitial pneumonia (21-24). Crystal *et al.* (18, 23) employed BAL for the evaluation of IPF and showed prominent increases in total cell numbers and proportions of neutrophils and/or eosinophils in BAL fluid. Furthermore, lymphocytes in BAL fluid were found to be increased in the early stage of IPF, while neutrophils were increased in the advanced stage (25, 26). This finding suggests that the lymphocytes found in BAL fluid may play some role in the initiation or regulation of the inflammatory process, which would initiate the fibrosing process, whereas neutrophils may enhance the process. In our study, patients in the active stage showed significantly higher proportions of neutrophils and eosinophils in BAL fluid than those in the non-active stage, also the survival of patients with more than 5 % neutrophils in BAL fluid was significantly shorter than those with less than 5 %. These findings indicate that BAL could be useful for evaluating the disease activity and prognosis of IIP. Patients with interstitial type III or IV had a significantly higher neutrophil percentages (5.4 ± 5.9 %) in BAL fluid than those with only type I or II shadows (2.0 ± 1.7 %). These findings also indicate that the neutrophils in BAL fluid can play some important role in the disease progression of IIP and that the percentage of neutrophils may be a good indicator of prognosis.

Only 10 %-30 % of patients with IPF or CFA have been reported to achieve objective improvement with steroid therapy (7-11). Tukiainen *et al.* (11) defined patients as responders when FVC increased more than 15 % above the initial value during 6 months of steroid therapy. We based our assessment of the effectiveness of steroid therapy on three parameters: grade of dyspnea, and levels of PaO_2 and FVC (% predicted). Patients showing improvement of more than one parameter were considered responders. Only one patient showed improvement of all three parameters. These findings confirmed the difficulty of improving the deteriorated pulmonary condition in IIP (UIP) with steroid therapy. The use of agents other than corticosteroids for the treatment of IIP has been controversial. Immunosuppressive agents such as azathioprine have been studied in IPF but whether or not they offer greater benefit than corticosteroids is questionable (27). Recently, it has been proposed that cytokines such as tumor necrosis factor (TNF) and transforming growth factor-β (TGF-β) may

be related to the fibrosing process in interstitial lung diseases. So, agents which inhibit these cytokines may be adopted as new forms of therapy of IIP in the future (27).

Rudd *et al.* (28) reported that responders were younger and had shorter disease duration before the treatment than non-responders; further, they found that responders had lower initial FVC (% predicted) than non-responders. Tukiainen *et al.* (11) and others (7–10, 28) have reported that patients achieving objective improvement with steroid treatment showed significantly longer survival than non-responders. In our study, although we found no significant difference in survival between responders and non-responders, the responders were younger and had a shorter disease duration before therapy, and they also had lower FVC and DL_{CO} (% predicted) values than non-responders. Moreover, all three of the responders at 6 months had shown acute exacerbation of the disease before therapy. These results suggested that steroid therapy may be effective in patients in whom the disease is of short duration and shows acute progression. An increase of lymphocytes in BAL fluid has been reported to be associated with good response to corticosteroid therapy, whereas an increase of eosinophils or neutrophils without a concomitant increase of lymphocytes, has been reported to reflect poor response (25, 29, 30). Furthermore, Schwartz *et al.* reported that excess eosinophils (more than 10 %) in BAL fluid are associated with disease progression and greater longitudinal decline in respiratory function (21, 30). On the other hand, Watters *et al.* (26) showed that neutrophil and eosinophil content in BAL fluid would not preclude corticosteroid responsiveness and could not be used as a reliable indication for making a therapeutic decision. Our study, however, revealed no significant difference between responders and non-responders in relation to cellular components in BAL fluid. It was, therefore, difficult to predict therapeutic effects before therapy, although several factors, *i.e.*, low FVC, low DL_{CO} (% predicted) and low PaO_2, indicating poor prognosis were correlated with good response to steroid therapy. In conclusion, in this study, interstitial shadows, pulmonary function, blood oxygen level, grade of dyspnea, neutrophil proportion in BAL fluid, and disease activity were shown to be significant prognostic factors in IIP. The evaluation of disease activity and cellular components in BAL fluid could be important for predicting the prognosis of IIP. However, it was difficult to predict the therapeutic effects of steroid treatment. We believe that, to evaluate the effects of steroid treatment in patients with IIP, it is necessary to carry out further studies on a larger population of patients in the active stage using controls to establish which variables, if any, are independent prognostic indicators.

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