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Factors influencing response to treatment of pulmonary tuberculosis.

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Abstract

We analyzed 150 patients with pulmonary tuberculosis from 1990 to 1996 (i) to evaluate the frequency of drug resistance, (ii) to elucidate factors influencing the response to chemotherapy, and (iii) to attempt to improve the therapeutic approach. Multidrug-resistant tuberculosis strains were not found. By univariate analysis, there were 8 factors associated with an increased sputum conversion time: male gender, prior treatment, complications, progressive chest radiographic findings, a high Ziehl-Neelsen stain score, lymphocytopenia, a high erythrocyte sedimentation rate (ESR), and hypoproteinemia. Complications, prior treatment, a high Ziehl-Neelsen stain score, and a high ESR were independent predictive factors in a Cox proportional hazard model. Recursive partitioning and amalgamation (RPA) defined 3 subgroups that responded to treatment. In order to reduce the time to sputum conversion, poor responders according to the RPA should be treated with a 4-drug regimen containing pyrazinamide.

KEYWORDS: drug-resistant tuberculosis, multivariate analysis, recursive partitioning and amalgamation (RPA)

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T he prevalence of multidrug-resistant (MDR) tuberculosis has increased in large cities in the United States. Immigration from Mexico, Haiti, Vietnam and China, as well as homelessness and infections due to the human immunodeficiency virus (HIV) have acted to increase the prevalence of MDR tuberculosis (1-5). Early in the chemotherapeutic era in the United States, 1 to 3 % of tuberculosis patients developed a drug-resistant strain of the disease; resistance was typically to a single drug. From 1982 through 1986, resistance to one or more antituberculosis drugs was found in 8.8% and 23% of previously untreated and treated tuberculosis patients, respectively (6-9). In Japan, HIV infection is rare and has not influenced the epidemiology of tuberculosis. The incidence of MDR tuberculosis in Japan was very rare until 1992; recently, resistance to isoniazid (INH) or rifampin (RIF) has been found in 15 to 20% of previously treated patients; resistance to both drugs has been found in 10% of these patients (10). We investigated the incidence of drug-resistant tuberculosis and its influence on therapeutic response. We examined how best to improve therapy and shorten the duration of inpatient hospitalization in cases of pulmonary tuberculosis.

Methods

We reviewed 150 patients with culture-positive tuberculosis; patients were hospitalized at Kure Kyosai Hospital between September 1, 1990 and September 1, 1996. The indirect drug susceptibility of all *Mycobacterium tuberculosis* strains was tested on 1% Ogawa egg agar according to the absolute concentration method using a microtiter technique developed by a commercial laboratory (BML, Tokyo, Japan). Concentrations of the antituberculosis drugs that were used in the susceptibility tests were as follows: INH: 0.1, 5 μg/ml; RIF: 5, 10, 50 μg/ml; streptomycin (SMP): 20, 200 μg/ml; ethambutol (EMB): 2.5, 5 μg/ml; aminosalicylic acid (PAS): 1, 10 μg/ml; ethionamide (TH): 25, 50 μg/ml; kanamycin (KM): 25, 100 μg/ml; viomycin (EVM): 25, 100 μg/ml; capreomycin (CPM): 25, 100 μg/ml; and cycloserine (CS): 20, 40 μg/ml. Critical concentrations were based on those used by the Japanese Society for Tuberculosis: INH, 1 μg/ml; RIF, 50 μg/ml; SMP, 20 μg/ml; EMB, 5 μg/ml; PAS, 1 μg/ml; TH, 25 μg/ml; KM, 100 μg/ml; EVM, 100 μg/ml; CPM, 100 μg/ml; and CS, 40 μg/ml. Drug-resistant strains were defined by complete resistance only. Sputum smears and cultures were performed on 3 consecutive days starting at admission. The highest score was regarded as the Ziehl-

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Neelsen stain score upon admission. During hospitalization, sputum specimens were collected for smear and culture every 2 weeks. Culture negativity was confirmed after no growth was detected for 8 weeks. Patients were hospitalized for 2 months after the sputum cultures had become negative. Almost all patients were treated with 3 drugs: INH, RIF, and SMP or EMB. Chest radiographic findings were divided into 3 classes: minimal, moderately advanced, and far advanced according to the National Tuberculosis and Respiratory Disease Association classification used in the United States (10). Medical risk factors included diabetes mellitus, silicosis, gastrectomy, malignancy, and chronic renal failure requiring dialysis (11, 12). Patients with positive acid-fast smears immediately received antituberculosis drugs. We found 109 patients with positive sputum smears; 7 of these patients were excluded from the final analysis (4 died of tuberculosis within 2 months after receiving therapy; 3 were lost contact with the hospital during the follow-up period). Of the remaining 102 patients, 85 were treated with INH, RIF, and SMP or EMB throughout their hospital stay; 17 had adverse reactions that led to a discontinuation of one or more of the medications. The time it took for the sputum culture to convert to negative was analyzed by the Kaplan-Meier method on a statistical software package, StatView version 4.5 (Abacus Concepts, Inc., Berkeley, CA, USA). Categorical data were compared with the generalized Wilcoxon test and the log-rank test. Multivariate analyses were performed with the Cox proportional hazard model using the stepwise regression method. A probability value of $P < 0.05$ was considered significant.

Results

Patient Characteristics and the Susceptibility Tests.

Table 1 presents the demographic and clinical characteristics of the 150 patients included in the study. Table 2 presents the results of the drug susceptibility analysis. Complete resistance to INH at 0.1 μg/ml or EMB at 2.5 μg/ml was found in 14.7% and 20% of the patients, respectively. Previously treated patients tended to be infected with more numerous drug-resistant strains. A 3-drug resistance to INH at 0.1 μg/ml, RIF at 10 μg/ml, and EMB at 2.5 μg/ml or SM 20 μg/ml was found in 5 of 150 patients. However, according to the critical concentrations from the Japanese Society for Tuberculosis, no cases of MDR tuberculosis were observed.

Time to sputum conversion.

A total of 102 patients with pulmonary tuberculosis and positive smears were eligible for the sputum conversion analysis (Table 1). The duration of hospitalization ranged from 2.1 to 31.3 months (the median stay in the hospital was 5.2 months). The response of patients with drug-resistant strains was compared to that of patients with drug-susceptible strains. There was no significant difference in the conversion time between the 15 patients with INH (0.1 μg/ml) resistance and the 81 patients with INH-sensitive strains. Six patients with EMB (2.5 μg/ml) resistance, 4 with RIF (10 μg/ml) resistance, and 2 with SMP (20 μg/ml) resistance also showed no significant differences in conversion time. Four patients with triple- (INH, RIF, and EMB or SMP) resistant strains also showed no difference in sputum conversion, as compared to the other 98 patients (Table 3). For these 4 patients, time to sputum conversion ranged from 2 to 14 weeks (median: 4 weeks);

Table I Demographic characteristics and clinical features of patients with culture-positive tuberculosis

Variable	All patients (N = 150)	Smear-positive patients (N = 102)
	No. of patients	
Age		
< 65 year	82	57
≧ 65 year	68	45
Sex		
Male	115	74
Female	35	28
Prior treatment of tuberculosis		
Yes	39	25
No	111	77
Complications[a]		
Positive	42	33
Negative	108	69
Radiographic findings[b]		
Minimal	27	17
Moderately advanced	74	45
Far advanced	49	40
Ziehl-Neelsen stain score		
Grade 2 or less	60	19
Grade 3 or more	90	83

a, Complications (No. for all patients/No. for smear-positive patients): diabetes mellitus (26/21), silicosis (6/5), gastrectomy (6/5), malignancy (3/2), and chronic renal failure on dialysis (1/0).
b, The National Tuberculosis and Respiratory Disease Association Classification in the United States in 1969.

Table 2   Drug susceptibility tests in 150 patients with pulmonary tuberculosis on admisson

Antituberculosis drug (resistant concentration, unit: μg/ml)	No. of patients showing complete drug resistance (%)		
	Previous treatment (n = 39)	No previous treatment (n = 111)	All (n = 150)
Isoniazid (5)	4 (10.3)	5 (4.5)	9 (6.0)
Isoniazid (0.1)	8 (20.5)	14 (12.6)	22 (14.7)
Rifampin (50)	0	1 (0.9)	1 (0.7)
Rifampin (10)	4 (10.3)	7 (6.3)	11 (7.3)
Streptomycin (20)	3 (7.7)	7 (6.3)	10 (6.7)
Ethambutol (5)	2 (5.1)	5 (4.5)	7 (4.7)
Ethambutol (2.5)	8 (20.5)	22 (19.8)	30 (20)
Aminosalicylic acid (1)	1 (2.6)	7 (6.3)	8 (5.3)
Ethionamide (25)	0	1 (0.9)	1 (0.7)
Kanamycin (100)	0	1 (0.9)	1 (0.7)
Viomycin (100)	0	0	0
Capreomycin (100)	0	0	0
Cycloserine (40)	0	0	0

these patients were men, aged 58 to 93 years. One of the 4 had undergone previous treatment, and 2 of the 4 had diabetes mellitus. Two had tuberculosis resistant to INH at 5 μg/ml, and all had tuberculosis resistant to RIF at 10 μg/ml, but sensitive at 50 μg/ml. Two of the 4 patients were treated with INH, RIF and EMB; one was treated with INH, RIF and SMP; and one was treated with KM, CS and PZA.

Univariate and Multivariate Analyses. By univariate analyses, 8 factors were significant in the time to sputum conversion: male gender, progressive chest radiographic findings (National Tuberculosis and Respiratory Disease Association (NTA) classification), complications, a Ziehl-Neelsen stain score of Grade 3 or more, lymphocyte count < 1000/mm³, previous treatment, ESR $\geq$ 70 mm, and serum protein < 6.5 g/dl (Table 3). With respect to complications, the univariate analyses addressed 3 major categories: silicosis (5 patients), diabetes mellitus (21 patients), and gastrectomy (5 patients). Diabetes mellitus was not associated with an increased conversion time, but silicosis and gastrectomy tended to be associated. Multivariate analysis showed that a high Ziehl-Neelsen stain score, complications, a high ESR, and previous treatment were independently associated with prolonged conversion duration. Complications were most strongly associated with increased conversion time (Table 4).

Recursive Partitioning and Amalgamation. The 102 patients with positive smears were divided into 3 groups according to their response to

chemotherapy; the method used was recursive partitioning and amalgamation (RPA) (13). The regression tree is shown in Fig. 1. Group 1 (36 patients) consisted of poor responders and contained 4 terminal nodes: A, complications and a high ESR (n = 12); B, complications, a low ESR, and previous treatment (n = 3); D, no complications, a high Ziehl-Neelsen stain score, far advanced chest radiographic findings, and male gender (n = 15); and E, no complications, a high Ziehl-Neelsen stain score, far advanced chest radiographic findings, and female gender (n = 6). Group 2 (50 patients) consisted of moderate responders, and included 2 terminal nodes: C, complications, a low ESR, and not having undergone previous treatment (n = 18); and F, no complications, a high Ziehl-Neelsen stain score, and moderately advanced (MA) or minimal (Min) chest radiographic findings (n = 32). Group 3 (16 patients) consisted of good responders, with 1 terminal node: G, no complications and a low Ziehl-Neelsen stain score (n = 16). The median conversion time was 12.5 weeks for group 1, 7.0 weeks for group 2, and 3.6 weeks for group 3 (Fig. 2).

Discussion

Approximately 43,000 new tuberculosis cases were registered in Japan in 1995. Although the incidence of tuberculosis was only 34.3 per 100,000 people in 1995 and has been gradually decreasing ever since the 1960s, the rate of decline has slowed since 1985, especially in persons younger than 40 years old (14). In 1995, there

Table 3   Univariate analyses of outcome of chemotherapy in 102 patients with pulmonary tuberculosis

Variable	No. of patients	Median duration of negative bacteriology (weeks)	Log-rank	Wilcoxon
Age				
< 65 year	57	7.8	NS	NS
≧ 65 year	45	8.8		
Sex				
Male	74	8.6	0.019	0.012
Female	28	5.4		
Prior treatment of tuberculosis				
Yes	25	13.0	0.034	NS
No	77	7.6		
Complications				
Positive	33	9.7	0.019	0.024
Negative	69	7.1		
Radiographic findings				
Minimal	17	5.5	0.007	0.016
Moderately advanced	45	7.1		
Far advanced	40	10.1		
Ziehl-Neelsen stain score				
Grade 2 or less	19	4.5	0.002	0.001
Grade 3 or more	83	8.8		
No. of lymphocytes				
< 1000/mm^3	35	10.9	0.018	NS
≧ 1000/mm^3	67	7.1		
ESR				
< 70 mm/h	59	7.1	0.015	0.026
≧ 70 mm/h	43	9.3		
Serum total protein				
< 6.5 g/dl	23	12.5	0.017	NS
≧ 6.5 g/dl	79	7.2		
INH 0.1 μg/ml resistance				
Yes	15	6.5	NS	NS
No	81	5.2		
RIF 10 μg/ml resistance				
Yes	4	7.2	NS	NS
No	91	7.4		
EMB 2.5 μg/ml resistance				
Yes	6	7.4	NS	NS
No	28	9.2		
SMP 20 μg/ml resistance				
Yes	2	4.1	NS	NS
No	62	8.2		
3-drug resistance				
Yes	4	4.0	NS	NS
No	98	7.8		

EMB, ethambutol; ESR, erythrocyte sedimentation rate; INH, isoniazid; RIF, rifampin; SMP, streptomycin.
NS, no significance.

Table 4   Cox multivariate analysis in 102 patients with pulmonary tuberculosis

Variables		Hazard ratio (95% CI)	P value
Complications	Yes vs No	2.27 (1.38–3.72)	0.001
Previous treatment	Yes vs No	2.21 (1.29–3.78)	0.004
Ziehl-Neelsen stain score	≧ 3 vs ≦ 2	2.04 (1.19–3.48)	0.009
ESR (mm/h)	≧ 70 vs < 70	1.85 (1.19–2.87)	0.006

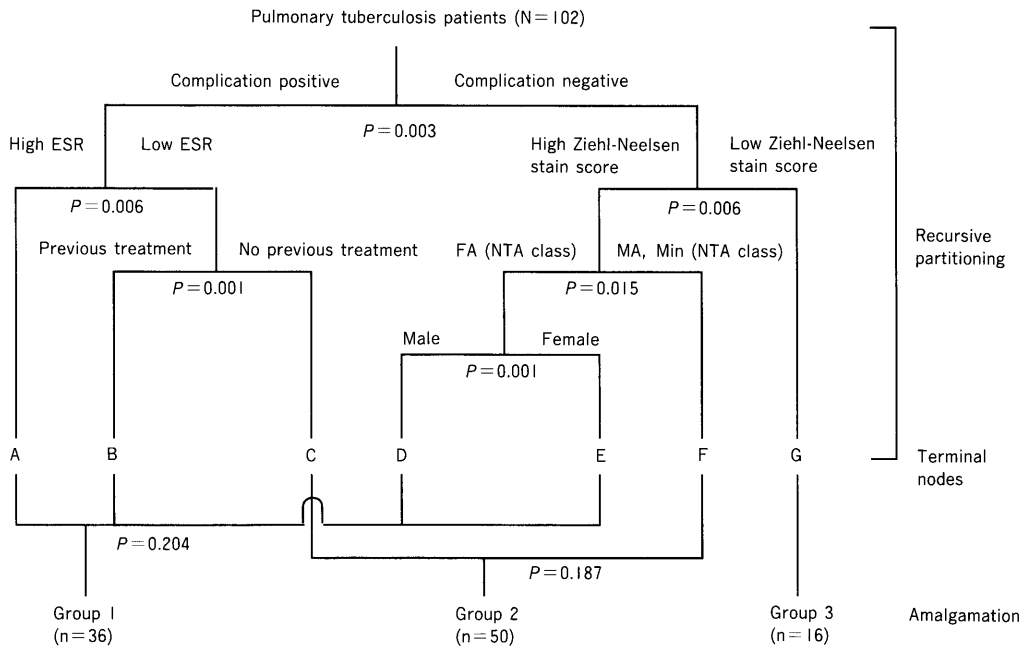ESR, erythrocyte sedimentation rate.
CI, confidence interval.

Fig. 1   Recursive partitioning and amalgamation (RPA) for 102 patients with pulmonary tuberculosis.
ESR, erythrocyte sedimentation rate; FA, far advanced; MA, modelately advanced; Min, minimal; NTA, National Tuberculosis and Respiratory Disease Association.
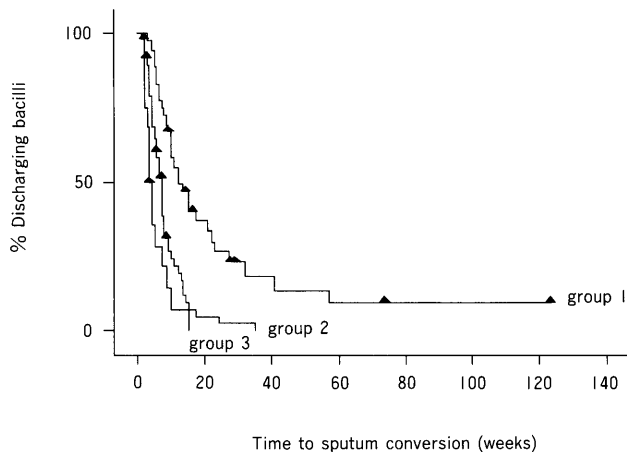
Fig. 2   Kaplan-Meier curves for the 3 homogeneous groups identified by the RPA analysis.
RPA, recursive partitioning and amalgamation.

were 3,200 deaths from tuberculosis in Japan (2.6 per 100,000 people). This rate is high compared with that of Western countries the same period. Concern is focused on older persons in particular. Certain geographic areas of Japan and infected non-Japanese among the Japanese population are also of increasing concern (15). It is important to achieve rapid sputum conversion to prevent the spread of infection.

An apparently limited increase in the incidence of tuberculosis in the United States was largely attributed to HIV infection; MDR tuberculosis has also become a major concern (1–5). The results of our study showed that the frequency of drug-resistant tuberculosis in our hospital was similar to nationwide results. INH or EMB resistance occurred more often in patients receiving initial treatment. Four patients had tuberculosis with resistance

to 3 drugs at the following doses: INH, 0.1 μg/ml; RIF, 10 μg/ml; and EMB, 2.5 μg/ml or SMP, 20 μg/ml. The time to sputum conversion in patients with resistance to 3 drugs did not differ from that observed in patients with drug susceptibility. Drug resistance, especially to RIF, was only moderate in these 4 patients, which perhaps accounts for the unaffected time to sputum conversion. At a concentration of 50 μg/ml, only 1 patient had tuberculosis resistant to RIF; there were no patients with MDR tuberculosis. Univariate analyses showed that the sputum conversion time was unrelated to monoresistance.

Multivariate analysis showed that a high Ziehl-Neelsen stain score, previous treatment, complications, and a high ESR were significant predictive factors for increased sputum conversion time, and that complications were the most predictive. Chest radiographic findings have been emphasized in the diagnosis, treatment, and management of tuberculosis in Japan until recently. In 1995, the Japanese public health council stressed that the activity classification of tuberculosis should consider the sputum burden (16).

In 1986, the American Thoracic Society and the Centers for Disease Control recommended 6 months of short-course chemotherapy consisting of INH, RIF, and PZA during the first 2 months and INH and RIF for the next 4 months as standard therapy for the initial treatment of pulmonary tuberculosis. This treatment regimen was endorsed by the International Union Against Tuberculosis and Lung Disease in 1988 and by the World Health Organization in 1991 (17–20). The Japanese Society for Tuberculosis endorsed a 4-drug short-course regimen containing PZA (INH, RIF, PZA and EMB or SMP) as one of the standard therapies in 1995. Recently, 3-drug chemotherapy with INH, RIF, EMB or SMP for 9 to 12 months has been preferred for smear-positive patients in Japan. This choice may reflect good patient compliance, long-term hospitalization, and caution regarding hepatotoxicity from high-dose PZA; these factors reduced the use of short-course regimens. Many randomized controlled trials have concluded that short-course regimens containing PZA shorten the time to sputum conversion; the conversion rate after 2 months of chemotherapy and the relapse rate after finishing chemotherapy were 71 to 95% and 0 to 3%, respectively; these results were superior to those of chemotherapy regimens that did not include PZA (21–25). Although it was not a randomized controlled trial, Wada and co-

workers reported similar results using a 4-drug short-course regimen containing PZA to treat 126 pulmonary tuberculosis patients (26). In another study, Aoki reported good results for a 4-drug 6-month course in patients with a high burden of organisms on their smears, as well as in patients who were thought to be relatively noncompliant (27). In conclusion, group 1 patients took an extremely long time to convert to negative cultures by the RPA method. A 4-drug, short-course chemotherapy treatment might have shortened the time to conversion and hospitalization in these patients. Since this study was retrospective and had a small sample size, further prospective studies of larger groups will be needed.

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