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Bronchoalveolar Lavage and Histopathologic Diagnosis Based on Biopsy

JMAJ 46(11): 469–474, 2003

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Abstract: The diagnostic significance of bronchoalveolar lavage (BAL) in idiopathic interstitial pneumonias (IIPs) is rather low, in that BAL merely enables exclusion of infections and such disorders as pulmonary alveolar proteinosis, which can be specifically diagnosed by this procedure, and suggests likelihood of eosinophilic pneumonia, BOOP or NSIP if assessments of cell fractions show an increase in eosinophils or lymphocytes alone. However, it is feasible to analyze disease states using components collected via BAL. In histopathologic diagnosis based on biopsy, it is impracticable to determine individual disease forms of IIPs by transbronchial lung biopsy (TBLB) because of the size of specimens obtainable, so surgical lung biopsy is required. Surgical lung biopsy procedures include open lung biopsy (OLB) and thoracoscopic lung biopsy. Lung biopsy with video-assisted thoracoscopy (VATS) is less invasive than OLB, and is performed in practically all applicable cases at present. For individual disease forms of IIPs, histopathologic diagnosis is currently carried out using this procedure at many medical institutions.

Key words: Bronchoalveolar lavage; TBLB; Surgical lung biopsy; Idiopathic interstitial pneumonia; Idiopathic pulmonary fibrosis

This article deals with "bronchoalveolar lavage and histopathologic diagnosis based on biopsy" as a current problem concerning interstitial pneumonia of unknown causes, i.e., idiopathic interstitial pneumonias (IIPs).

Bronchoalveolar Lavage

As for bronchoalveolar lavage (BAL) in IIPs (Fig. 1), to begin with, the BAL technique is an examination method initially devised in the 1970's that can be said to be epochal, and has been progressing with the development of fiberbronchoscopy. Bronchus of the relevant lung segment are irrigated in the case of a localized lesion, or the middle lobe of the right lung or the left lingular segments are lavated in patients with diffuse lung diseases. The procedure is

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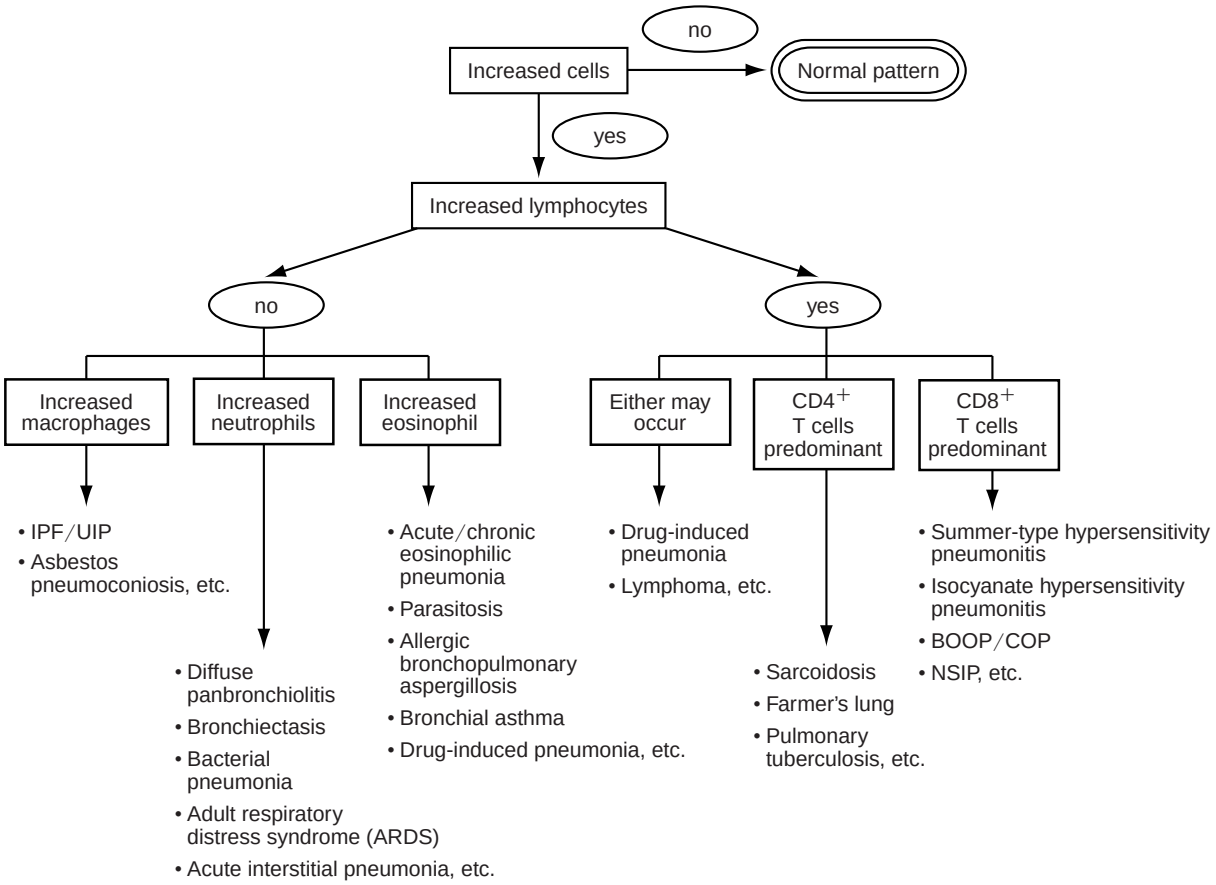

Fig. 1 Differentiation of diffuse lung diseases based on BAL findings

that the tip of a fiberbronchoscope is wedged into the target bronchus and a total volume of 100–200 m*l* of lukewarm physiological saline fluid is injected through that endoscope in aliquots of 20–50 m*l*, followed by collection of the lavage fluid. The first collection of fluid may not be used for examination because it eventually contains high concentrations of regional components of the airway.

The lavage fluid yield is usually about 60%. If the recovery rate is extremely low, it becomes difficult to evaluate BAL findings. Liquid components and cellular components in the collected BAL fluid specimen are examined and used for diagnosis and research. From the diagnostic viewpoint, the condition best indicated by BAL is pulmonary alveolar proteinosis, for which a whitish turbid liquid reminiscent of rice grain washings is obtained and is definitely diagnostic. The procedure is employed for specific diagnosis of alveolar hemorrhage, infections such as tuberculosis, mycosis, and *Pneumocystis carinii* pneumonia, asbestos pneumoconiosis verified by demonstrating asbestos bodies in the lavage fluid, pulmonary Langerhans' cell histiocytosis (granulomatosis) diagnosed by noting increased CD1-positive cells, or malignant tumors.[1)]

Other conditions where BAL is relatively highly useful for diagnosis include chronic or acute eosinophilic pneumonia where a marked increase of eosinophils is observed in the lavage fluid, sarcoidosis in which there is a marked increase in lymphocytes with elevated CD4/8 ratio (when supported by other findings), and summer-type hypersensitivity pneumonitis simi-

larly with markedly increased lymphocytes yet with lowered CD4/8 ratio.

An important point in making evaluations of BAL findings is that the cellular pattern changes with cigarette smoking, and in interpreting BAL findings one needs to consider whether the subject under test is a smoker or a non-smoker. One should exercise caution in that an increased cell population collected in lavage fluid with an increase in percent macrophages, a decrease in percent lymphocytes and a decreased CD4/8 ratio are noted in healthy smokers, hence presenting a cellular pattern different from that seen in non-smokers.

Next I would like to discuss the usefulness of BAL from the angle of diagnosis of IIPs. Firstly, the usefulness of BAL consists in that the above-mentioned specific diseases can be excluded by analysis of BAL fluid from among a variety of diseases that present diffuse opacities in the lungs. It is infeasible, nevertheless, to make a diagnosis of IIPs on the grounds of BAL findings, nor is it possible to diagnose various disease forms of IIPs. The usefulness of BAL as a research tool is unquestioned, but the value of BAL from the viewpoint of diagnosis is limited.

In idiopathic pulmonary fibrosis (IPF), the central clinical entity among IIPs, it is generally recognized that the BAL cellular pattern is macrophage-predominant and close to a normal pattern. Furthermore, an increase in neutrophils by ≥5% is observed in 70–90% of patients with this disorder, and an increase in eosinophils by ≥5% is noted in 40–60% of patients. Besides these changes, an increase in lymphocytes is demonstrable in only 10–20% of patients, and an increase in lymphocytes alone is noted in less than 10%.[1)]

If there is only an increase in lymphocytes, therefore, it may be said that other disorders than IPF should rather be suspected, such as sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans with organizing pneumonia (BOOP), nonspecific interstitial pneumonia (NSIP), or lymphoid interstitial pneumonia (LIP). In cases, especially where the increased lymphocytes mostly comprise CD8-positive cells with a CD4/8 ratio of ≤1, BOOP or NSIP would be more likely than other IIPs and further differentiation between them according to lung imaging pattern may be possible.

The next problem to be discussed is whether BAL can be utilized for prognostic estimation. This, too, has limitations as regards IPF. Some reports suggest that the prognosis is unfavorable in patients showing increased percentages of neutrophils and/or eosinophils, but these reports are not authoritatively supported. Increased lymphocytes are observed in less than 20% of cases of IPF as mentioned above, and it is generally recognized that the increase in lymphocytes on BAL correlates with cellular infiltration type in biopsied specimens, responses to corticosteroids can be anticipated, and honeycomb lung is rare. BAL is not so invasive as an examination but there have been a report that acute exacerbation occurred due to BAL;[2)] it is not a frequently repeatable procedure. Therefore, the cellular pattern on BAL performed as part of initial diagnostic evaluation may possibly be useful for prognostic estimation, but will require technical skill at the institution and scrupulous care in the interpretation of results.

Thus, BAL is used solely for the limited purpose of excluding other disorders in the diagnosis of IIPs. However, studies on the disease state of various diffuse lung diseases have been making rapid progress thanks to gene analysis using cells collected by means of BAL and analysis of components in the BAL fluid. The role of BAL in pathophysiologic studies of IIPs may be said to be extremely prominent.

Transbronchial Lung Biopsy

This section deals with transbronchial lung biopsy (TBLB) (Table 1). Specimens obtained by TBLB are quite small, measuring up to 5 mm in diameter. It is difficult consequently to accurately determine the extent of fibrosis or

Table 1 Comparison of Transbronchial Lung Biopsy and Surgical Lung Biopsy

	Transbronchial lung biopsy	Surgical lung biopsy	
		Video-assisted thoracoscopy	Open lung
Invasiveness	Slight (to moderate)	Moderate	Marked
Anesthesia	Local anesthesia	General anesthesia	General anesthesia
Operation time	Short	Short	Rather long
Identification of sampled lesion	Rather difficult	Easy (difficult at times)	Easy
Direct observation of lesion	Difficult	Feasible (difficult at times)	Feasible
Frequency of diagnosis	Repeatable	Limited to once	Limited to once
Tissue specimen collected	Extremely small	Ample	Ample
Complication	Occasional (ca. 10%)	Occasional (ca. 10%)	Occasional (ca. 2.5–7%)

(Cited, with modification, from Respiratory Disorders—New Approach 1 *In* Bandoh, S. and Sugiyama, Y.: *Indications for Endoscopy (Bronchoscopy and Thoracoscopy), Approaches to Diagnosis Based on Symptomatology*. Medical View, Tokyo, 2001, pp. 77–83)

inflammation and its pattern, and it is impossible to pathologically differentiate disease forms of IIPs from such TBLB specimens.[3)] With the specimens obtained by TBLB, however, it is feasible to definitely rule out in the first place such granulomatous lung diseases as sarcoidosis, hypersensitivity pneumonitis and pulmonary Langerhans cell histiocytosis, infections by tubercle bacilli or mycotic agents, various malignant tumors or malignant lymphomas, eosinophilic pneumonia, and pulmonary alveolar proteinosis.

There is also the possibility that BOOP, among other IIPs, may be diagnosed to some extent by TBLB because of its characteristic pathologic features. Tissues at the peripheral alveolar level immediately subjacent to the pleura are sampled under fiberbronchoscopy. More concretely, the biopsy forceps are advanced to immediately subjacent to the pleura under fluoroscopic control with the patient holding his/her breath once, then the forceps are pulled back a little and opened, and the tissue is sampled in harmony with patient's breathing motion. It is a common practice to biopsy the site possibly best reflecting the disease on imaging in diffuse lung diseases as well, with S^{3a} and S^{8a} usually being chosen for the biopsy.

TBLB also is not so invasive as an examination but is impracticable in a patient unable to hold his/her breath for a short time due to coughing or hypoxemia. There have been cases in which acute exacerbation of IPF followed TBLB-associated pneumothorax; here too, needless to say, caution must be observed.

Surgical Lung Biopsy

The following surgical lung biopsy procedures are to be undertaken in further focusing the diagnosis after disorders specifically diagnosable by BAL and/or TBLB have been excluded. Surgical lung biopsy procedures include open lung biopsy (OLB) and thoracoscopic lung biopsy, including lung biopsy with video-assisted thoracoscopy (VATS). Both procedures are performed under general anesthesia, and lung biopsy is carried out using VATS in practically all cases currently because it is less invasive and requires shorter durations of drainage and hospital stay. A marked advance made in recent years has been that, with the development of VATS, surgical lung biopsy can now be performed far more easily.

The purpose for which surgical lung biopsy is carried out is to attain an ultimate histopathologic diagnosis in a patient whose diffuse

lung disease has not been diagnostically ascertained by BAL and/or TBLB. As disease forms of IIPs cannot be diagnosed by BAL and/or TBLB, surgical lung biopsy is aimed at determination of the disease form. The primary objective is thus to differentiate between IPF generally unresponsive to steroid therapy (histologically, usual interstitial pneumonia: UIP) and NSIP, desquamative interstitial pneumonia (DIP) or BOOP/COP (cryptogenic organizing pneumonia) which are usually responsive to steroid therapy. However, there is a high degree of possibility of IPF/UIP in chronic cases where IIPs are suspected with typical image findings and obvious honeycomb lung features on high-resolution CT (HRCT) scan. The diagnostic strategy usually does not proceed up to VATS in such cases. In IIPs, VATS may be said to be an examination performed to obtain histopathologic evidence to ascertain indication for steroid therapy in patients in whom IPF/UIP has been ruled out.

IPF is precisely defined as a disease presenting histopathologic features of UIP. Pathologically, the disease is generally recognized to be characterized by diverse phases of changes with a patchy, especially subpleural, distribution of lesions with the presence of honeycomb lung and fibroblastic foci. In NSIP reported by Katzenstein *et al.* in 1994,[4] in contrast, lesions are diffuse and temporally homogeneous with characteristically concordant phases and respond well to steroid therapy, thus differing in these respects from IPF.

As regards the group III (fibrotic type) of NSIP, problems have often arisen for histopathologic features in the differential diagnosis from UIP, and opinions vary even among pathologists. The issues are still to be clarified.

It is generally thought that the points described below should be taken into account in order to improve the certainty of pathologic diagnosis in undertaking VATS.

As for the problem of tissue sampling sites, it has been suggested that it is most desirable to take samples from three different sites, i.e., the area of the most pronounced lesion, the area where the most incipient change is likely to be present, and an area of intermediate change.[5] It is generally thought advisable that apical regions of the middle and lower lobes, where nonspecific subpleural collapse often occurs, are to be avoided. Specimens obtained by VATS are a few cm in size, hence more than 10 times as large as those sampled by TBLB, and therefore can provide information that enables determination of the distribution of lesions (patchy or diffuse), their relation to the airway, and the destruction/modification pattern of alveolar structures. Only with this approach, it is possible to differentiate histologic patterns among such entities included in IIPs as UIP, NSIP, DIP, acute interstitial pneumonia (AIP), BOOP/COP and respiratory brochiolitis-interstitial lung diseases (RB-ILD), and thus to permit an ultimate diagnosis. However, there are still conditions which cannot be placed under any of the above-mentioned histologic patterns, even by the surgical biopsy VATS. Such conditions have to be taken as unclassifiable. One should note that VATS is not an omnipotent examination.

As is the case with BAL or TBLB, there have been clinical cases of IIP in which acute exacerbation occurred due to surgical lung biopsy including VATS, thus one must stress the need for careful consideration in applying this technique. Risk factors involved in surgical lung biopsy have been described as excluding patients over 70 years of age, and patients with intercurrent cardiac disorders, markedly depressed pulmonary function, and severe obesity.[1]

We have reviewed above the roles of bronchoalveolar lavage, transbronchial lung biopsy, and surgical lung biopsy especially as means of diagnostic approach in cases of idiopathic interstitial pneumonias.

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Limitations of Corticosteroids and Cytotoxic Agents in Treating Idiopathic Pulmonary Fibrosis

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Abstract: Although anti-inflammatory drugs such as steroids and cytotoxic agents have been used to treat idiopathic pulmonary fibrosis (IPF), these conventional anti-inflammatory therapies do not improve its outcome, probably because fibrosis is not preceded or provoked by alveolitis. A new therapeutic strategy aimed at suppressing abnormal fibroproliferative responses needs to be verified in Japanese patients with IPF.

Key words: Idiopathic pulmonary fibrosis; Steroid therapy; Cytotoxic agents; Anti-Fibrotic agents; Immune modulators

Introduction

Among the various types of interstitial pneumonias, alteration of the natural history of idiopathic pulmonary fibrosis (IPF) by therapeutic interventions has met with limited success, resulting in an extremely poor prognosis. This paper outlines issues involved in the treatment of IPF.

Problems with Previous Studies on the Treatment of IPF

Idiopathic pulmonary fibrosis (IPF) is a type of idiopathic interstitial pneumonia that progresses to widespread interstitial fibrosis and irreversible destruction of lung architecture. IPF histologically exhibits a patchy interstitial scarring process that emanates from the subpleural areas and septa, and also is characterized by both the presence of aggregates of fibroblasts, termed fibroblastic foci, and honeycomb formation of lung (Table 1).

The treatment of IPF is frustrating because no established therapeutic regimen supported by convincing evidence currently exists. Problems found in studies on the treatment of IPF (Table 1) include (1) a lack of randomized

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Table 1 Idiopathic Pulmonary Fibrosis and Problems in Clinical Studies

Features of idiopathic pulmonary fibrosis
• One type of idiopathic interstitial pneumonia
• Patchy distribution of variegated lesions from inflammation to scarring
• Aggregates of fibroblasts
• Destruction of lung architecture that emanates from subpleural areas with honeycomb change
• Progressive nature
Problems with therapeutic studies of idiopathic pulmonary fibrosis
• Insufficient investigation using randomized placebo-controlled studies
• Inadequate numbers of patients in case-control studies
• Possibility of misdiagnosis of nonspecific interstitial pneumonia (NSIP) as IPF

placebo-controlled trials demonstrating the significance of steroids and immunosuppressants such as cyclophosphamide, (2) insufficient numbers of patients studied to date, and (3) confusion with nonspecific interstitial pneumonia (NSIP), i.e., prior to the introduction of the concept of NSIP in 1994, some cases of NSIP were confused with IPF, leading to overestimation of the effects of steroids or immunosuppressants, partly because those with NSIP that is more responsive to steroids have a significantly better outcome than those with IPF. This confusion is likely to remain a problem, since some cases of NSIP can not be differentiated from IPF. Key features in the histologic diagnosis of IPF include the presence of aggregates of actively proliferating fibroblasts and honeycomb lung. However, no consensus currently exists among pathologists as to the degree to which the findings of these features are acceptable when making a diagnosis of NSIP. These problems have led researchers to point out various drawbacks in previous studies. As noted above, the greatest drawback is that no randomized controlled study has been carried out in Japan to indicate the efficacy of steroid and immunosuppressant therapies.

Relevance of Evidence-Based Medicine from the U.S. and Europe to Japanese Patients with IPF

The concept of evidence-based medicine (EBM) proposed in the 1990s has had a revolutionary effect on the practice of medical care.[1] A critical question posed by EBM, however, is that of how results reported in the literature should be applied to actual patients. Nevertheless, the prevailing trend is for emphasis to be placed on the evidence itself. An important issue to be aware of is whether the characteristics of the population presented in the literature are the same as those of the patients who are actually being treated. In other words, to what extent are results reported in the literature relevant to the individual patients that we see.[2]

From this point of view, it would be desirable for a randomized controlled study to be carried out in Japan, in the event that race-related differences might be present. For instance, there is room for discussion as to whether steroid therapy that is efficacious against certain diseases in Caucasians is also of benefit in Japanese people, who generally have less glucose tolerance. It is also unclear whether the relative ratios of the molecular species of the drug-metabolizing enzyme cytochrome P-450 are the same among patients of different races.

Patients with IPF Amenable to Treatment

What types of patients are amenable to treatment once a diagnosis of IPF has been established? The answer to this question varies, as there are differences of opinion on how to determine the propriety of treatment for individual patients. Because of the current lack of effective treatment based on definitive evidence, one suggestion is that patients be followed throughout the course of their illness and treatment be considered when a downhill course is observed.

Table 2 Patients with Idiopathic Pulmonary Fibrosis Indicated for Treatment

The Consensus Statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommends that treatment be initiated in all patients with IPF who do not have contraindications, because the prognosis of idiopathic pulmonary fibrosis is poor. (Although the response rates of currently available treatments are low, patients in the early stage of disease may benefit from treatment.)

1. Patients who have worsening clinical findings or findings on imaging.
2. Patients who have a 20% or higher proportion of lymphocytes in bronchoalveolar lavage fluid.
3. Patients in whom a diagnosis of collagen disease has not been established but is suggested by clinical symptoms and blood test data.
4. Patients whose condition is difficult to distinguish from nonspecific interstitial pneumonia (NSIP).
5. Patients in whom histologic examination has revealed areas showing histologic features other than those of usual interstitial pneumonia (UIP).

Table 3 Considerations Regarding Indications of Treatment

1. Since idiopathic pulmonary fibrosis has a poor prognosis, treatment should be given if it outweighs treatment-related complications.
2. Given the limited success of current treatments, patients in the early stage of IPF may respond better to treatment.
3. Caution is necessary in patients with the following characteristics, which are liable to lead to treatment-related complications: age over 70 years, extreme obesity, concomitant major illness such as cardiac disease, diabetes mellitus, or osteoporosis, severe impairment in pulmonary function, end-stage honeycomb lung.
4. Prednisolone at a dose of 0.5 mg/kg/day should be given for 4 weeks, followed by a reduced dose of 0.25 mg/kg/day for 8 weeks, then tapering to 0.125 mg/kg/day.
   At the same time, cyclophosphamide (2 mg/kg/day) or azathioprine (2–3 mg/kg/day) should be combined.

(From the International Consensus Statement. *Am J Respir Crit Care Med* 2000; 161: 646.)

On the other hand, as noted in the Consensus Statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), the view is held by some that treatment should be performed in all patients unless there are contraindications to therapy, because IPF has a poor prognosis. The statement also suggested that the response rate might increase among patients who receive treatment in an early stage of the disease.[3)]

In various institutes, including ours, the natural course of patients with IPF is usually followed after the diagnosis has been established. However, treatment is considered in cases such as those listed in Table 2.[4)] More specifically, a treatment is initiated when the clinical manifestations, chest radiographs, and/or pulmonary physiology deteriorate during follow-up; when the proportion of lymphocytes in bronchoalveolar lavage fluid is in excess of 20%; when there are clinical symptoms and blood test findings not documenting but suggesting collagen disease; and when there is difficulty in differentiating the patient's condition from NSIP.

Even specimens obtained by surgical lung biopsy do not always reflect histologic changes in the entire lung. We often encounter inconsistency in findings from different sites of the lung. If the features of usual interstitial pneumonia (UIP) are found in one area, it is appropriate to diagnose the case as UIP or idiopathic pulmonary fibrosis.[5)] However, when there are histological changes other than those of UIP, the area has a fair chance of responding favorably to treatment and therefore warrants positive consideration for intervention.

Treatment of IPF Patients

As indicated in Table 3, particular attention

Table 4 Summary of Clinical Studies of Idiopathic Interstitial Pneumonia and the Results of Treatment

Year	Author	No. of subjects	No. of patients given steroid therapy	Response rate (No. of patients)
1960	Scadding	26	12	8.3% (1) Slight improvement in 4 cases
1964	Livingstone	45	31	6.5% (2) Slight improvement in 5 cases
1965	Stack	42	31	13% (4)
1978	Carrington	53	26	11.5% (3)
1978	Winterbauer	20	20	60% (12)
1980	Turner-Warwick	220	Four-year survivors were observed in 18% of ineffective cases and 40% of untreated cases	
1983	Tukiainen	113	100	30.3% (in 4 years)
1987	Guerry-Force	18	14	14.3% (2)
1987	Watters	26		37% (7/19)
1989	Johnson	Double-blind study. Three-year survival P : P + C = 55% : 86%		
1991	Raghu	Double-blind study. Nine-year survival P : P + A = 23% : 57%		

P: prednisone or prednisolone, C: cyclophosphamide, A: azathioprine.

Table 5 Double-Blind Studies on Treatment of Idiopathic Interstitial Pneumonia

- 1989, Johnson, M.A., Turner-Warwick *et al.*
  (*Thorax* 1989; 44: 280–288)
  22 patients received prednisolone monotherapy (initially 60 mg, reduced to 20 mg every other day).
  21 patients received cyclophosphamide (100–120 mg) and prednisolone (20 mg every other day).
  The disease was refractory to both therapies, but prognosis was better in the latter group. (3-year survival, 55% vs. 86%)
- 1991, Raghu, G., Winterbauer, R.H. *et al.*
  (*Am Rev Respir Dis* 1991; 144: 291–296)
  13 patients received prednisone monotherapy (1.5 mg/kg/day for 2 weeks, followed by 20 mg/day).
  14 patients received azathioprine (3 mg/kg/day) and prednisone (1.5 mg/kg/day for 2 weeks, followed by 20 mg/day).
  After adjusting for age, results were significantly better in the latter group (9-year survival, 23% vs. 57%).

is required when the patient has certain characteristics that are vulnerable to treatment-related complications, i.e., age over 70 years, extreme obesity, cardiac disease or diabetes mellitus, osteoporosis, severe impairment in pulmonary function, and end-stage honeycomb lung. At present, the recommended treatment is oral prednisone [not available on the Japanese market; almost equivalent to prednisolone (Predonine®)] at a daily dose of 0.5 mg/kg combined with cyclophosphamide (Endoxan®) or azathioprine (Imuran®) at a daily dose of 2 mg/kg. The background for this recommendation includes data such as those presented in Table 4. The response rate for steroid monotherapy in previous case studies has generally ranged from 10–20%.

Steroids are considered to exert their effects through inhibition of the production of monocyte chemoattractant protein-1 (MCP-1) from bronchial epithelia and activated macrophages; inhibition of interleukin-8 (IL-8), which is important for the migration and activation of neutrophils; and inhibition of the production of various cytokines from activated T lymphocytes. In clinical cases, however, the efficacy of steroid monotherapy unfortunately has not met our expectations. It is reported that patients given no treatment sometimes achieve better survival rates than those who are given treatment but do not respond to it (see, for example, the report of Turner-Warwick, 1980).

Double-blind studies comparing steroid monotherapy and combined steroid and immunosuppressant therapy have revealed that the combined therapy is more effective (Table 5). More specifically, Turner-Warwick's group compared 22 patients treated with prednisolone monotherapy (initial dose 60 mg, reduced by 5 mg every week, to a regimen of 20 mg every other day) with 21 patients given a combination of cyclophosphamide (100–120 mg) and prednisolone (20 mg every other day). The results showed a tendency to better prognosis with the latter therapy, although the disease was refractory in both groups.[6] The 3-year survival rate was reported to be 55% in the prednisolone monotherapy group while it was 86% in the combined therapy group.

Raghu *et al.*[7] compared prednisone monotherapy (1.5 mg/kg/day for 2 weeks, followed by a 20 mg/day maintenance dose) in 13 patients with combined therapy consisting of azathioprine (3 mg/kg/day) and prednisone in 14 patients. After adjusting for age, prognosis was better with the combined steroid and immunosuppressant therapy; the survival rate at 9 years was 23% for those given prednisone monotherapy and 57% for those given prednisone in combination with azathioprine.

In summary, it seems that combined steroid and immunosuppressant therapy is usually more effective than steroid monotherapy. However, even the combined therapy achieves a response rate of only about 30%. Therefore, it remains questionable whether combined therapy is effective enough to significantly improve the prognosis of IPF.

The results of a questionnaire survey demonstrated that Japanese physicians specializing in respiratory diseases often employ symptomatic therapy when a diagnosis of IPF is made. The practical measures are used partly because assessing patients' responsiveness to monotherapy or combined therapy requires a considerable amount of time, at least several months. In the future, it is expected that the use of serum markers for IPF, such as KL-6 and SP-D, will make it possible to evaluate the assessment of responsiveness more easily.

Table 6 Alternative and New Treatments

Colchicine
Tranilast
Neutrophil elastase
Erythromycin
Angiotensin-converting enzyme inhibitors
Acetylcysteine
Interferon γ-1b
Interferon β-1a
Pirfenidone (S-7701)
Soluble TNF receptor (etanercept)

Practical Alternative Treatments Available in Japan

The use of cyclophosphamide as a high-dose pulse intravenous regimen has been reported recently. This regimen consists of intravenous cyclophosphamide (10–20 mg/kg) repeated every 4 weeks. It reportedly is associated with lower incidences of adverse reactions such as hemorrhagic cystitis and malignant tumor, and at the same time allows reduced doses of steroid to be used.

It has also been reported that combination therapy with cyclosporin (Sandimmun®, Neoral®) and steroid improved both pulmonary function and dyspnea. The oral absorption of cyclosporin varies greatly among individuals. This necessitates measurement of the trough level just before dosing, and the goal should be set at about 100–150 ng/m*l*. Since cytochrome P-450 is largely involved in the metabolism of this agent, caution is necessary because of possible interactions with combined drugs. Tacrolimus is also being considered from the standpoints of efficacy and reduced adverse effects.

In addition to the above agents, colchicine,[9,10] tranilast, neutrophil elastase, erythromycin, ACE Inhibitor, and N-acetylcysteine as an anti-oxidative stress drug[11] have been tried either as monotherapy or in combination therapy (Table 6).

Colchicine was expected to be effective because of its inhibitory effect on the release of fibroblast growth factor from macrophages, and its efficacy in retrospective studies has been reported. However, in a study of high-dose steroid therapy and colchicine therapy, high-dose steroid was associated with serious adverse reactions, decreased lung function, and decreased survival time, while colchicine therapy was not effective.

Therapeutic attempts using interferon have been attracting attention. In a study of 18 patients with IPF unresponsive to conventional treatment, 9 patients each were randomly assigned to interferon γ-1b therapy (200μg, 3 times a week, subcutaneously) in combination with prednisolone (7.5 mg/day) or prednisolone alone (7.5 mg/day), and followed for 12 months.[12] The results demonstrated that the patients given interferon γ-1b showed better improvement in vital capacity and arterial oxygen tension both at rest and under loading.

The efficacy of interferon β-1a was also examined.[13] A total of 167 patients with IPF were randomly assigned to four groups to be given placebo (43 cases) or intramuscular interferon β-1a twice weekly at a dose of 15μg (42 cases), 30μg (41 cases), or 60μg (41 cases). The results indicated that interferon β-1a was not effective.

Ongoing Therapeutic Studies

Although no collected data on treatments for IPF are available in the Cochrane Database of Systemic Reviews, the following two protocols are currently in progress. One is a study by the Cochrane Airway Group to examine the efficacy of steroid therapy, and the other is a randomized controlled study of cyclophosphamide to analyze mortality, respiratory symptoms, arterial blood gas, frequency of hospitalization, exercise tolerance, and quality of life (QOL). When the results of these studies become available, they are expected to provide firm ground for the propriety of using steroids and cyclophosphamide in the treatment of IPF.

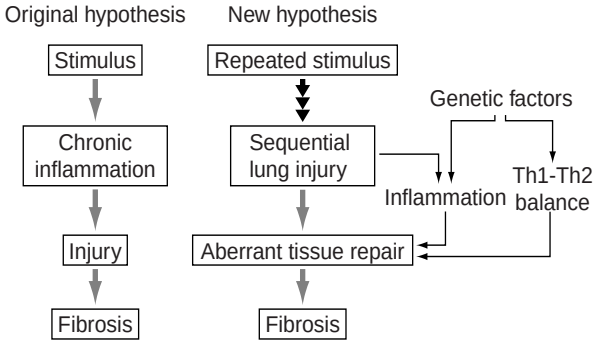

Fig. 1 Hypotheses explaining the pathology of idiopathic pulmonary fibrosis
(Adapted from Gross, T.J. *et al.*: *New Engl J Med* 2001; 345: 517)

In addition, a double-blind parallel-group placebo-controlled study of S-7701 (pirfenidone) has been carried out to determine its efficacy and safety in patients with chronic-type IPF, providing data that suggest the efficacy of this therapy.[14]

It is well known that in cases of rheumatoid arthritis TNFα (tumor necrosis factor α) is produced from activated macrophages and is involved in inflammation. To inhibit the action of TNFα, the use of TNF receptor as a therapeutic agent has been attempted. TNF receptor is divided into two types according to molecular weight, 55 kDa and 75 kDa. Etanercept is a recombinant protein in which TNF receptor p75 is fused to the Fc portion of human IgG1. A preliminary study in 9 patients showed that it was effective in inhibiting aggravation of pulmonary function.[15]

From Inflammation to Epithelial Injury

The process by which chronic inflammation leads to chronic injury with subsequent fibrosis was commonly considered the core concept in the pathophysiology of IPF. However, histologic findings of cellular infiltration that can be called alveolitis are rare in surgically biopsied lung specimens from IPF patients.

Selman *et al.*,[16] who examined the relation

between inflammation and fibrosis, concluded that inflammation is not indispensable to the development of fibrosis, based on the fact that there was a lack of association between the degree of inflammation and fibrosis in various animal experiments and that fibrosis can be elicited by epithelial injury alone in the absence of inflammation. This has led to the understanding that chronic inflammation is not the essential factor in determining prognosis, but that fibrosis occurs as a result of epithelial injury and defects in the subsequent healing process. Emphasis is now placed on the concept of epithelial-fibroblastic disease (Fig. 1),[16,17] and therefore treatments such as those listed in Table 6 are currently being reviewed and reevaluated.

In Closing

In ending this paper, the author would like to stress the need for prudence in accepting data from Western countries as evidence for EBM. A randomized controlled study on this issue, which would be the first in Japan, is of extreme importance. However, such a study is not yet feasible under current circumstances in Japan. In order to promote patients' understanding of such studies, efforts aimed at the disclosure of pertinent information would be desirable.

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Idiopathic Pulmonary Fibrosis
—Possible new treatments and recent clinical trials—

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a chronically progressive fatal disease. However, as there are no prospects of successful prognostic improvement by currently available methods, the development of effective new treatments to improve prognosis is eagerly awaited throughout the world. Although much remains to be elucidated as to the pathology of IPF, it is understood according to two processes: lung injury resulting from preceding inflammation and fibrosis caused by abnormal repair. Most conventional therapies, including steroid therapy, have focused on the inhibition of inflammation. However, the inhibition of fibrosis itself has been attracting recent attention, and clinical applications are evolving. This paper describes the current status of clinical trials of interferon therapy ongoing in Western countries, with an explanation of its mechanism of action. In addition, the progress of a clinical trial of pirfenidone, the first randomized placebo-controlled study on the drug treatment of IPF in Japan, is described. Various treatment strategies for IPF suggested by basic research are also introduced.

Key words: Idiopathic pulmonary fibrosis; Anti-fibrotic therapy; Anti-inflammatory therapy; Pirfenidone; Interferon; N-acetylcysteine

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic type of idiopathic interstitial pneumonia. Currently about 2,300 patients in Japan are receiving medical subsidies for this condition,[1)] but the actual number of patients with the disease is estimated to be 5,000 to 10,000, including those who have not sought medical consultation. Since IPF is a progressive, fatal disease for which no spontaneous cure exists, elucidation of its pathology and the development of therapies are urgently needed, even though it is a rare disease. The current situation is such that some physicians are reluctant to treat patients when a diagnosis of idiopathic

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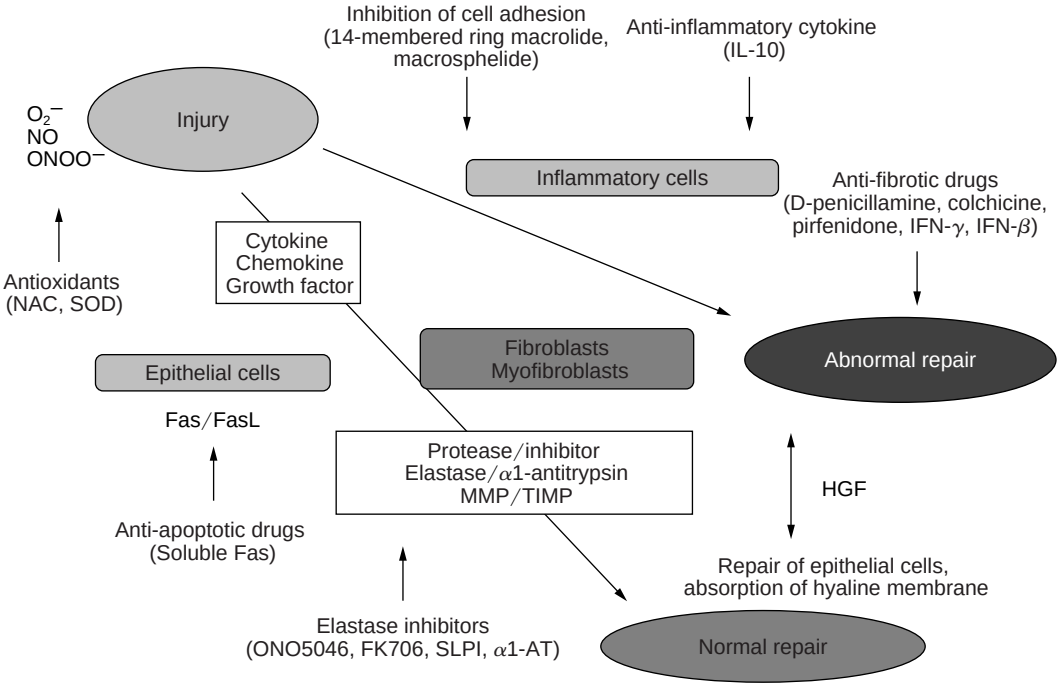

Fig. 1 Schema of the pathological features of pulmonary fibrosis and new therapeutic strategies: repair and reconstruction following lung injury
(Originally designed by Toshihiro Nukiwa from the Research Committee on Diffuse Pulmonary Disease, Ministry of Health and Welfare)

pulmonary fibrosis is made, since no effective treatment to improve prognosis is available.

The existing treatment for IPF aims only at temporary improvement of symptoms and pulmonary functions, because no effective measures are known for improving the prognosis. Therefore, future treatments are being sought both in Japan and other countries.

Treatment Rationale (Fig. 1)

Idiopathic pulmonary fibrosis (IPF) is considered to be a condition in which inflammation precedes tissue injury and results in fibrosis in lung tissue that is unable to carry out normal restoration.[2] The cause of inflammation is unknown, and the subsequent repair process may be insufficient or abnormal, leading to fibrosis. Another feature of IPF is that it develops and progresses with aging. Therefore, it is important to elucidate the mechanisms of aging. Conventional treatments have been restricted to the inhibition of various factors in the inflammatory process.[3] However, the efficacy of immunosuppressive treatment including steroid therapy is limited to temporary symptomatic relief.

In recent years, the propriety of these treatments has been reconsidered, and the lack of reliable clinical trials and absence of established criteria for the evaluation of treatment have been cited as faults of previous evaluations.

In light of these circumstances, we have categorized the therapeutic interventions for IPF into the following five areas: (1) inhibition of aggravation caused by acute exacerbation, (2) inhibition of chronic inflammation, (3) inhibition of chronic progressive fibrosis, (4) transplantation, and (5) regenerative medicine. Ongoing development of new treatments focuses primarily on items (1) to (3). These devel-

Table 1 Recent Clinical Trials on Idiopathic Pulmonary Fibrosis

Drug	Study design	Study period	Observation items	Results	Publication
• Interferon-γ	Incremental to prednisolone ($n=9:9$)	12 months	TLC, Pa_{O_2} (at rest), Pa_{O_2} (during maximum exercise)	Effective	Ziesche, R. *et al.*: *New Eng J Med* 1999; 341: 1264–1269.
• Interferon-β	Randomized double-blind controlled trial	12 months	Survival time, FVC, Pa_{O_2}	Ineffective	Raghu, G.: ATS 2001 (San Francisco)
• Pirfenidone	Open-label ($n=54$)	24 months	Survival time, FVC, TLC, DLco, Sp_{O_2}, etc.	Effective	Raghu, G. *et al.*: *Am J Respir Crit Med* 1999; 159: 1061–1069.
• Colchicine	Comparison against prednisolone ($n=12:14$)	30 months	Survival time, adverse effects	No significant difference	Douglas, W.W. *et al.*: *Am J Respir Crit Care Med* 1998; 158: 220–225.
• Colchicine	Three drugs including prednisolone	70 months	Survival time, FVC, TLC	No significant difference	Selman, M. *et al.*: *Chest* 1998; 114: 507–512.
• N-acetylcysteine	High-dose, oral therapy	12 weeks SHt, Met(0)	Bronchoalveolar lavage: cells, respiratory function: comparison against 4 months before therapy	Effective	Behr, J. *et al.*: *Am J Crit Care Med* 1997; 156: 1897–1901.

TLC: total lung capacity, Pa_{O_2}: arterial oxygen tension, FVC: forced vital capacity, DLco: carbon monoxide diffusion capacity

oping treatments will be outlined, with reference to future perspectives.

Development of New Treatments

The following paragraphs describe the status of recent European and North American clinical trials concerning IPF (Table 1).

In 1999, a European group reported the efficacy of interferon (IFN)-γ in 9 patients with IPF. The incremental benefit of IFN-γ 200μg (given three times per week subcutaneously) combined with prednisolone for 12 months was examined in comparison with prednisolone monotherapy. Results showed significant improvement in lung function in terms of %FVC, alveolar-arterial oxygen gradient (A-aDo_2), and total lung capacity (TLC) (Fig. 2).[4)]

In the same year, an open-label trial of the oral antifibrotic agent pirfenidone ended, achieving inhibition of deterioration in lung function.[5)]

In 2000, the protocol of a double-blind randomized controlled study of IFN-β in North America was presented at the annual meeting

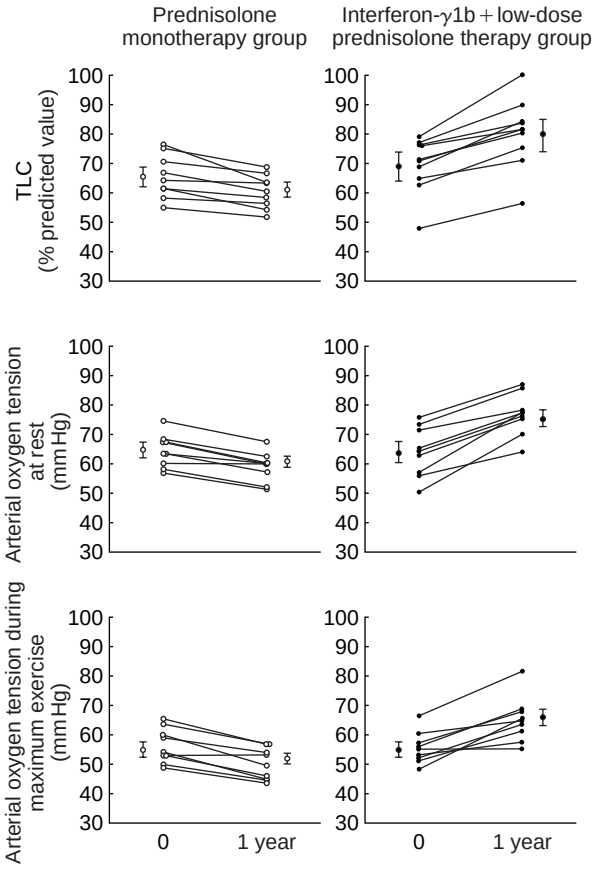

Fig. 2 Results of interferon-γ therapy for idiopathic pulmonary fibrosis
(From Ziesche, R. *et al.*: *N Engl J Med* 1999; 341(17): 1264–1269)

Table 2 Endpoints for Evaluation in Clinical Trials of Pirfenidone in Japan

The efficacy of pirfenidone therapy and that of a placebo were examined to determine which was more effective.
1) Primary endpoint
(1) Changes in Spo_2 from baseline during the 6-min walk test.
2) Secondary endpoints
(1) Changes in resting Pao_2 from baseline.
(2) Changes in lung function parameters (VC, TLC, DLco) from baseline.
(3) Changes in markers (KL-6, SP-D) from baseline.
(4) Changes in findings on diagnostic imaging (chest radiography, high-resolution CT) from baseline.
(5) Changes in chronic respiratory disease questionnaire score (HR-QOL index) from baseline.
(6) Changes in signs and symptoms (degree of dyspnea, cough, and sputum).

Table 3 Protocol of the Six-Minute Treadmill Walk Test at a Constant Speed

• The subject undergoes the walk test on a treadmill.
• The treadmill speed should be set at an appropriate rate for each subject prior to the study, according to the given procedure, and measurements are obtained using the same speed.
• Walking speed should be fixed at 40, 50, 60, or 80 m/min, with 60 m/min being the standard speed.
• It is preferable to obtain measurements while recording time-course changes in Spo_2 every 10 sec.
• In view of safety, the test should be discontinued when Spo_2 is 85% or less for 30 consecutive sec, or when Spo_2 rapidly decreases to less than 80%.

of the American Thoracic Society (ATS) in Toronto, and the progress of the long-term study, which extended over 2.5 years, was reported. However, at the 2001 ATS meeting, Professor Raghu, G. from the University of Washington reported that IFN-β therapy showed no benefit either for lung function or survival time. In his overall comments, he concluded that therapeutic potential cannot be expected from IFN-α or -β, whereas IFN-γ appears promising.

Clinical Trials in Japan

1. Pirfenidone

Pirfenidone, which was examined in an open-label study in the US, is one of the most promising agents for IPF (Table 2). This agent exerts inhibitory activity on the production of a number of inflammatory cytokines, including tumor necrosis factor (TNF)-α,[6] and also inhibits the collagen synthesis.[7] Therefore, a clinical trial of this drug as an antifibrotic agent was carried out in the US, targeting IPF.[5] In Japan, a double-blind randomized controlled study of pirfenidone for IPF was begun in November 2000 to verify its efficacy and safety.[*8]

Pirfenidone was developed by MARNAC, Inc., of the US. In Japan, Shionogi & Co., Ltd., acquired a license for production from MARNAC, and a clinical trial was initiated. After about six months of study using a daily oral dose of 1,200–1,800 mg, an interim analysis was performed in 2001. Because of the decrease in acute aggravation among patients on pirfenidone therapy, the agent was assessed as effective. Adverse effects such as photosensitivity and gastrointestinal symptoms were noted, as in the clinical trial in the US. These effects, however, were considered to be controllable by adjusting the dosage. On the basis of these clinical trial data, an application for the approval of pirfenidone's use in Japan was sent to the Ministry of Health, Labor and Welfare.

One of the special features of the above study was its attempt to provide an exploratory evaluation of drug efficacy (Table 3). In previ-

ous clinical studies on the treatment of IPF, a period of 1 or 2 years was required for investigation, and drug efficacy was evaluated in terms of improvement in static lung function. IPF is a chronic progressive disease with an extremely slow course.

Because of this limitation, we attempted to more sensitively detect changes in lung function by quantifying the decrease in blood oxygen saturation during exercise as an area and using it as a primary endpoint (a modification of the original method developed by N. Tsuboi and K. Nakata, Respiratory Division, Toranomon Hospital). The conventional six-minute walk test is associated with individual changes in walking speed and walking distance along with improvement of lung function, making it difficult to compare pre- and post-treatment status accurately. In contrast, exercise with constant speed loading before and after treatment in the above study allowed more accurate evaluation of therapeutic efficacy. Although there is room for improvement in this method of evaluation, it is expected to be applied more widely as a sensitive, objective method of evaluating the efficacy of new drugs.

2. Interferon (IFN)

Owing to the circumstances referred to previously, IFN-β therapy for IPF was judged to be ineffective at the 2001 ATS meeting. In light of this evaluation, clinical trials of IFN-β therapy were abandoned in Japan. However, since IFN-γ is expected to be effective in preclinical studies and the results of an earlier pilot study were promising,[4] the introduction of clinical trials employing this therapy is now under consideration in Japan, awaiting the publication of results of an ongoing large-scale clinical trial of IFN-γ in North America.

3. N-acetylcysteine (NAC)

The Research Committee on Diffuse Pulmonary Disease of the Ministry of Health, Labor and Welfare is in charge of clinical investigations of NAC inhalation therapy as well as other therapies. This therapy is expected to inhibit injury to the alveolar epithelium through its antioxidant properties. NAC attracted general attention in 1997, when Behr *et al.* in Germany reported improvement in lung function after high-dose oral NAC therapy (1,800 mg/day in 3 divided doses).[8] In Japan, an inhibitory effect on the progression of pulmonary fibrosis is expected from inhalation therapy with nebulized injectable NAC.

In an open-label trial in Japan, inhaled NAC provided improvement in clinical symptoms in comparison with the baseline in 30% of patients who were on this therapy for at least one year and was rated "effective" in about 40% of the patients. In addition, no particular adverse effects occurred after prolonged use, demonstrating its safety (Ishii *et al.*, Ministry of Health and Welfare Research Project).

In Europe (7 countries), a large-scale clinical trial of NAC therapy is underway in about 150 patients with IPF, using vital capacity and DLco as primary endpoints, based on the data reported to date.

4. Cyclosporin A (CYA)

In contrast to the conventional treatment of pulmonary fibrosis by anti-inflammatory drugs, attempts have been made to use cyclosporin A therapy, with a stronger effect expected as a result of its immunosuppressive activity. Its therapeutic efficacy in general cases of pulmonary fibrosis is under investigation, and no decisive conclusion has yet been reached.

However, it appears that some patients with rapidly progressive interstitial pneumonia caused by collagen disease who have not responded to prednisolone (PSL), cyclophosphamide (CPA), or azathioprine (AZP) are rescued by CYA therapy.

On the other hand, steroids have been used to treat the acute exacerbation of IPF, but results have been extremely poor. Accumulated clinical evidence indicates that the combined use of CYA for this condition provides a favorable response, preventing re-aggravation

as a result of the reduced dosage of steroid therapy (Yoshizawa *et al.*, Ministry of Health and Welfare Research Project).

Future verification by a larger-scale clinical trial is awaited.

Therapeutic Targets Expected from Molecular Pathological Research

Although the targets of pulmonary fibrosis treatment are broadly divided into "lung injury" and "fibrosis," there is a question as to what therapeutic strategies are possible.

Treatment to inhibit lung injury caused by inflammation, i.e., the inflammatory phase, has depended on steroids or immunosuppressants. In recent years, however, gene therapy to supplement the cytokines that are lacking has been tried in an attempt to correct the imbalance of inflammatory conditions in the body.

1. Inhibitory effect of IL-10 on interstitial pneumonia

The inhibitory activity of interleukin (IL)-10 is one of the promising treatment options; *in vivo* gene transfer has achieved inhibition of inflammation and fibrosis of the lung in the bleomycin (BLM)-induced lung injury model.[9] In addition, in the *in vitro* setting, IL-10 inhibited transforming growth factor-β (TGF-β)-induced production of collagen in fibroblasts.

Based on the above findings, it is apparent that IL-10 is an important inhibitory factor for both inflammation and fibrosis of the lung, and the possibility of introducing IL-10 therapy for IPF patients is now being examined from its fundamental aspects.

2. Anti-fibrotic action of 14-membered ring macrolides

Macrolide antibiotics represent a class of drugs that have recently been attracting attention because of their anti-inflammatory effect on airway inflammation. In preclinical studies, this class of antibiotics inhibited tissue infiltration and injury by neutrophils as well as inhibiting airway inflammation, suggesting beneficial effects in the inhibition of fibrosis.[10]

On the other hand, lung tissue in which the existing architecture has been destroyed and replaced by fibrosis can never be restored. Thus regeneration and reconstruction of the alveolar epithelium in the tissue injury phase is considered a critical process in the normal repair mechanism.

3. Clinical application of gene therapy with hepatocyte growth factor for pulmonary fibrosis

Hepatocyte growth factor (HGF) is a promising epithelium-regenerating factor.[11] Currently, the development of efficient HGF expression vectors and their introduction to the lung are being attempted in the experimental setting. However, the greatest problem involved in such gene introduction is whether the possibility exists of maintaining gene expression in the right quantity and in the right place. Thus, technical issues remain to be solved.

Future Perspectives

ATS indicated in the international consensus statement entitled "Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment" published in its official journal in 2000 that a change from conventional therapeutic strategies is necessary. Attention has already been focused on the inhibition of fibrosis itself rather than the inhibition of inflammation, which has been the key point in conventional treatments. However, for some drugs, the results of clinical and experimental studies have not necessarily been consistent.

Diagnostic issues regarding IPF are also in the process of reevaluation. The pathological condition of IPF may present different clinical pictures according to its temporal phase. Future discussion should be advanced from the stage of drug discovery to that of treatment guidelines based on close investigations.

Although gene therapy has been introduced

for several diseases, the induction of gene expression in appropriate quantities required according to time and place remains a key issue to be solved in gene therapy for IPF in view of the peculiarity of the disease site, namely, the respiratory organ. To this end, it may be important for medical care of the 21st century to examine the possibility of tailored treatment based on full knowledge of the individual patient's characteristics, including the developmental stage of the lung.

In addition, from the viewpoint of regenerative medicine, it is important to be able to induce regeneration of lost alveolar epithelial cells where it is required. These studies are about to begin, and a vision created on the basis of an international perspective will be needed.

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Idiopathic Pulmonary Fibrosis
—Acute exacerbation and lung cancer associated with pulmonary fibrosis—

JMAJ 46(11): 490–496, 2003

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Abstract: The 5-year survival rate for idiopathic pulmonary fibrosis (IPF) is 30–50%, and the major causes of death are respiratory failure, cardiac failure, lung cancer, infection, and pulmonary thromboembolism. Clinical conditions of acute exacerbation of IPF, which was first reported from Japan and is also now being recognized in Europe and the US, include deterioration of dyspnea, exacerbation in image findings, a decrease in the partial pressure of oxygen in arterial blood, and elevation in the levels of KL-6 and SP-D, in a short period of time. Its clinical characteristics are those of the ARDS and its pathological findings are those of diffuse alveolar damage (DAD). Infection, an inappropriate tapering of the dose of steroids, certain medications, invasive tests, and surgical operations are among the inducing factors. Combination therapy by steroid pulse and cyclosporin-A has been attracting attention. The complication of lung cancer in IPF, which is frequently observed in patients aged 70 or older, is one of the prognostic factors, and the knowledge of IPF is indispensable to treat this. Expression and mutations of various genes during the repairing process of damaged DNA is presumed to be involved in the development of this lung cancer. Special attention is required for the treatment because surgery, administration of anti-cancer drugs, and radiation can possibly induce the acute exacerbation.

Key words: Idiopathic pulmonary fibrosis; Acute exacerbation; Cyclosporin-A; Complication of lung cancer; Microsatellite

Introduction

Idiopathic pulmonary fibrosis (IPF) is a slowly progressive disease with poor prognosis, and the mean survival time and 5-year survival rate have been reported to be 2–4 years and 30–50%, respectively.[1)] If the total survival rate is considered, the 5-year survival rate appears

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The Japanese text is a transcript of a lecture originally aired on April 10, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

Table 1 Acute Exacerbation of Idiopathic Pulmonary Fibrosis (definition)

"Acute Exacerbation" can be diagnosed when deterioration of dyspnea, bilateral ground glass attenuation/opacification appear or become more pronounced on a chest radiograph, and a significant decrease in partial pressure of oxygen in arterial blood are observed within 1 month of clinical course of idiopathic pulmonary fibrosis. Obvious lung infection and cardiac failure are excluded.

Related findings:

(1) CRP or LDH often increases.

(2) Both the extent and distribution of the ground glass attenuation/opacification can be elucidated by chest CT.

(Cited from *the Annual Report for Fiscal 1994 by the Research Committee on Diffuse Lung Diseases, the Ministry of Health and Welfare,* 1995; 9–11)

higher since there are patients who survive longer, while the 5-year survival rate of new patients was 30%.[2] As the cause of death in IPF patients, respiratory failure is most frequent at roughly 40%, followed by cardiac failure, lung cancer, infection, and pulmonary thromboembolism.[3]

Acute Exacerbation of IPF

1. Pathology and diagnosis

Within a short period of 1 month, bilateral ground glass attenuation/infiltrative opacification develops or is accelerated on a chest radiograph and respiratory failure ensues and worsens. Exacerbation of respiratory failure due to cardiac failure or infection should be excluded for this definition. In Europe and in the USA, the acute worsening of respiratory failure was considered to be the natural history of IPF, and was not recognized as acute exacerbation. A recent review of the new IPF guidelines from the American Thoracic Society (ATS) showed that the term acute exacerbation was included, suggesting the possibility of increasing recognition of the proposal from Japan.[4] In Japan, acute exacerbation has long been recognized as an important disease process related to prognosis for survival in the clinical course of IPF, and the Research Committee on Interstitial Lung Diseases of the Ministry of Health and Welfare has focused on the pathogenesis of IPF and the development of new therapeutic methods to treat this condition.[5]

The pathogenesis of acute exacerbation of IPF where respiratory failure worsens within a short period of time and is refractory to therapy with a high mortality rate, has been investigated from various aspects to reveal its clinical profile.[6] According to the definition (Table 1) of the Research Committee on Diffuse Lung Diseases of the Ministry of Health and Welfare, the diagnosis of "acute exacerbation" can be made when all of the following signs are observed within 1 month of the clinical course: (1) deterioration of dyspnea, (2) bilateral ground glass attenuation/infiltrative opacification appears or becomes more pronounced on a chest radiograph, (3) a significant decrease in partial pressure of oxygen in arterial blood. Definitive pulmonary infection and cardiac failure should be excluded from the definition.[5] To date, the increase in CRP (C-reactive protein) and LDH have been considered related findings, but recently KL-6, SP-D, and SP-A have been used as markers more specific to interstitial pulmonary diseases. These markers might be used in the future instead of LDH as related findings.

KL-6, a kind of free mucin, is a large molecular glycoprotein classified in MUC1, and is a marker which reflects the alveolar damage that occurs as a result of inflammation, rather than inflammation itself. SP-D and SP-A are surfactant proteins and are produced by the type II alveolar epithelium. They have been considered markers which reflect alveolar damage

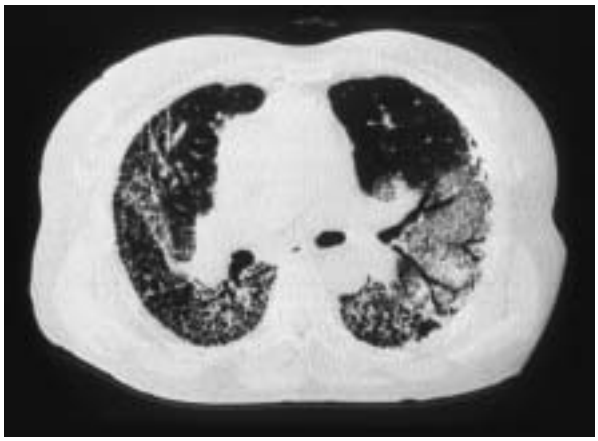

Fig. 1 HRCT findings of acute exacerbation

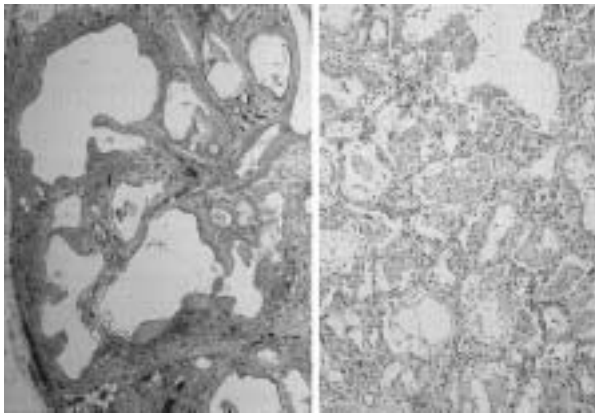

Fig. 2 Diffuse alveolar damage

similar to KL-6. The definition includes appearance or deterioration of bilateral ground glass attenuation/infiltrative opacification on a chest radiograph, while chest CT shows more detailed findings. Chest CT, especially high-resolution CT (HRCT) is now an essential diagnostic tool.

The extent and distribution of ground glass attenuation are seen clearly and accurately on chest CT. In particular, the results obtained by high-resolution CT (HRCT) are invaluable, and may predict the response to steroid therapy. HRCT of acute exacerbation which illustrates diffuse ground glass attenuation or infiltrative opacification is shown (Fig. 1).

In Europe and America, the concept of acute exacerbation is not well recognized, and it has been considered the progression of respiratory failure based upon the natural clinical course of IPF. Acute exacerbation has been considered the final stage of respiratory failure after a long clinical course, since it has been reported that there are no differences in the mean survival time between the patients who succumbed to acute exacerbation of IPF and those patients who succumbed after gradual progress of respiratory failure.[7] However, there has been an increasing recognition of acute exacerbation in IPF as a characteristic disease process in Europe and USA[4,8,9] through the vigorous exchange of information with Japan.

Table 2 Causes Which May Induce Acute Exacerbation of Idiopathic Pulmonary Fibrosis

1. Infection
2. Inappropriate tapering of the dose of steroids
3. Use of drugs which induce interstitial pneumonia
4. Invasive examination/treatment (TBLB, BAL, surgery, etc.)
5. Radiation exposure
6. Pneumothorax

Acute exacerbation is the acute lung injury superimposed on pulmonary fibrosis which includes advanced honeycomb lung. The histologic findings are characteristics of diffuse alveolar damage (DAD). DAD is an acute inflammation which is characterized by hyaline membrane formation and its exudative and proliferative phases (Fig. 2). The cause of IPF itself is unknown, and the pathogenesis of acute exacerbation has not been elucidated. Prior to the onset of acute exacerbation, the lung might be preset to release various inflammatory mediators. Therefore, acute lung injury is induced when the following causes or factors are encountered.[10,11]

Acute exacerbation can be induced by a number of factors which include an inappropriate tapering of the dose of steroids, surgical lung biopsy (VATS, etc.), transbronchial lung biopsy (TBLB), bronchoalveolar lavage

(BAL), the use of drugs which induce interstitial pneumonia (especially anticancer drugs), radiation exposure, general anesthesia, and surgical operation (Table 2). The respiratory failure aggravated obviously by infection is excluded, but the negation of the involvement of viral infection is difficult.

2. Treatment

Therapeutic options for the treatment of IPF have not been clearly established, and the data from prospective randomized clinical trials does not support the efficacy of the empirical use of steroids.[12] In addition, the prognosis of acute exacerbation of IPF remains poor. Therefore, the conventional regimen for the treatment of acute exacerbation is methylprednisolone (Solu-Medrol®) at a daily dose of 500–1,000 mg for 3 consecutive days with concomitant administration of an immunosuppressant such as cyclophosphamide (CPA) when the steroid pulse therapy is ineffective. Data from a multi-center trial of a total of 32 patients with acute exacerbation of IPF (selected according to the diagnostic criteria proposed by the Research Committee on Diffuse Lung Diseases, the MHW), showed no significant differences in the therapeutic modalities, including the dose of steroids, between the patients who succumbed to the disease and those who survived.[10]

Since 1995, IPF patients in our department with acute exacerbation have been treated with cyclosporin-A (CYA), an immunosuppressant, from the early stage,[13] in addition to the steroid pulse therapy, even though it is not covered by health insurance. Four out of 7 patients are still alive, and they did not experience any episodes of re-exacerbation during the tapering of the dose of steroids,[14] while all patients who did not receive CYA eventually succumbed to the disease. Subsequently, in response to questionnaires, it was learnt that 15 (75%) of 20 patients who were administered CYA at a total of 10 hospitals through the whole country succumbed to acute exacerbation, and the efficacy of CYA was not clear. Timing of initial administration and the dose of CYA is different for each patient. Consequently, a multicenter prospective study was considered necessary to assess the efficacy of CYA, and the study is now being planned.

In all cases, treatment of acute exacerbation of IPF is difficult. In addition to the elucidation of the pathogenesis of this condition and its refractoriness to treatment are issues that remain to be resolved.

Complication of Lung Cancer

The frequency of complication by lung cancer in advanced IPF is high and the elucidation of the mechanism by which lung cancer develops in IPF is expected to lead to a better understanding of oncogenesis in general lung cancer. In IPF complicated by lung cancer, the diagnostic procedures and treatment choice for lung cancer are limited and have become the subject of clinical discussion.

1. Mechanism of complication of lung cancer

The frequency of complication of lung cancer in IPF is known to be in the range of 10–15% in general,[1] although 30% or more have been reported in patients aged 70 years or older. Whether IPF itself is a risk factor for the development of lung cancer remains controversial, since complication of lung cancer in IPF was more frequently observed in smokers. At present, it is recognized that IPF is an independent risk factor for the development of lung cancer.[15]

The molecular mechanism of the development of lung cancer in IPF is unclear. Chronic DNA damage occurs in IPF and the enhanced expression or mutation of various genes may take place during repair. For example, in the bronchial epithelium or pulmonary alveolar epithelium, particularly at the severe metaplastic loci of an IPF patient, expression of p53, a cancer-suppressor gene, or p21, a cell cycle regulator, has been reported.[16] These expressions might be inhibiting oncogenesis during

the repair of DNA leading to normal repair. Highly frequent alterations of p53 protein as a result of enhanced expression of the p53 gene are well known in IPF.[17] Furthermore, the serum anti-p53 autoantibody directed toward accumulated p53 altered protein has been detected in IPF.[18]

In general, the inhibition of cancer-suppressor genes is considered an important step in oncogenesis. A microsatellite marker, a polymorphism marker scattered in the genome, has been effectively used in investigation/identification of unknown cancer-suppressor genes. The locus amplified by polymerase chain reaction (PCR), which is a method to amplify a specific gene locus and to make it detectable by using the microsatellite marker, is highly polymorphic and heterozygous. The loss of one arm of a chromosome containing this locus is expressed as a loss of heterozygosity (LOH). When the microsatellite locus for analysis in non-cancerous tissue contains cancer-suppressor genes, existence of LOH indicates that this non-cancerous tissue is in the pre-cancerous stage.

The author and colleagues microscopically dissected the metaplastic epithelium of IPF patients complicated with lung cancer and evaluated LOH using the microsatellite marker in the short arm of the 3rd chromosome (3p), which is implicated to contain cancer-suppressor genes, to detect LOH frequently.[19] In addition, it has been reported that the results of the sputum of IPF patients analyzed using the microsatellite markers at 10 loci scattered in the 8th, 9th and 17th chromosomes showed LOH at least at one locus of the chromosomes in approximately 40% of the patients.[20] Instability of chromosome replication in cancer cells was observed in the microsatellite locus as the difference in the length of repeated sequences, and is known as microsatellite instability. In the analysis of the sputum of IPF patients, it is reported that approximately 20% of the patients showed microsatellite instability in at least one area.

Therefore, the tendency for an IPF patient to develop lung cancer might be explained by gene abnormalities which occur during the process of the repair of chronic DNA damage.

2. Treatment of lung cancer associated with IPF

If an IPF patient has lung cancer as a complication, conventional options of treatment such as surgery, radiation treatment, or chemotherapy are considered. However, as mentioned above, it should be noted that any of these treatments may induce acute exacerbation. Although the frequency of acute exacerbation attributed to surgery is reported to be at a 10% level,[21] oxygen at high concentration, high tidal volume, and anesthesia, in addition to surgical invasion, may also induce the exacerbation.

On the other hand, since ventilation is maintained by one lung with a respirator during surgery, tissue damage due to ischemia-reperfusion may happen when sudden bilateral ventilation of the lungs is introduced immediately after completion of surgery. Furthermore, an IPF patient with lung cancer might not be a candidate for surgical operation due to decreased pulmonary functions. Radiation treatment is the therapy which might induce acute exacerbation with the highest frequency, and its application is very limited.[23,24] In general, as compared to radiation treatment, chemotherapy has been considered less likely to induce acute exacerbation of IPF. However, drugs which may cause drug-induced interstitial pneumonia should not be administered. It is necessary to note that new anti-cancer drugs, which recently have been frequently used, should be carefully administered to patients having interstitial pneumonia or pulmonary fibrosis as an underlying disease [ex. gemcitabine (Gemzar®) and irinotecan (Topotecin®) are contraindicated, and vinorelbine (Navelbine®), docetaxel (Taxotere®), and paclitaxel (Taxol®) require careful monitoring during administration]. Also, it should be noted that administration of

steroid pulse therapy concomitantly with anticancer drugs corresponds to the inappropriate tapering of the dose of a steroid, and is a risk factor of acute exacerbation.

The above is an overview of acute exacerbation and lung cancer associated with IPF referring to prognosis for survival of a patient with IPF (idiopathic pulmonary fibrosis). The pathogenesis and treatment of this condition have not yet been established. Future development of research in this area is expected.

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Current Status of Esophageal Cancer Treatment

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Abstract: The diagnosis and treatment of esophageal cancer has made remarkable progress in Japan. In terms of diagnosis, the number of early-stage superficial cancer cases detected by panendoscopy and iodine staining has increased, depth of cancer invasion can be diagnosed by EUS, the diagnosis of lymph node metastasis is becoming commonplace, and the diagnosis of tumor malignancies using a molecular biology approach has greatly advanced. In terms of treatment, treatment for mucosal cancer using endoscopic mucosal resection (EMR) has become widespread, the outcome of treatment has improved (5-year survival rate of more than 60%) as a result of the wider use of radical surgery with three-field (neck, chest, and abdomen) lymphadenectomy, chemoradiotherapy regimens have been reviewed, and the use of prosthesis insertion in inoperable cases has increasing rapidly. In particular, esophageal cancer is now classified as a curable cancer, thanks to improvements in the safety and performance of radical surgery. Some issues that require further investigation include improvements in the accuracy of detecting lymph node metastasis and prospective diagnoses of individual chemosensitivity.

Key words: Esophageal cancer; Endoscopic mucosal resection (EMR); Radical esophagectomy with three field lymph node dissection

Introduction

Recently, a rapidly increasing number of early-stage superficial esophageal cancers are being detected, thanks to improvements in diagnostic techniques for these cancers, especially the widespread use of panendoscopy and iodine staining. To determine an appropriate course of treatment for superficial esophageal cancers (mucosal [m] and submucosal [sm] cancers), a precise diagnosis regarding the depth of cancer invasion and the presence of lymph node metastasis is essential. In particular, determining whether endoscopic mucosal resection (EMR) is indicated is necessary to establish the lesion category: m1/m2 (from

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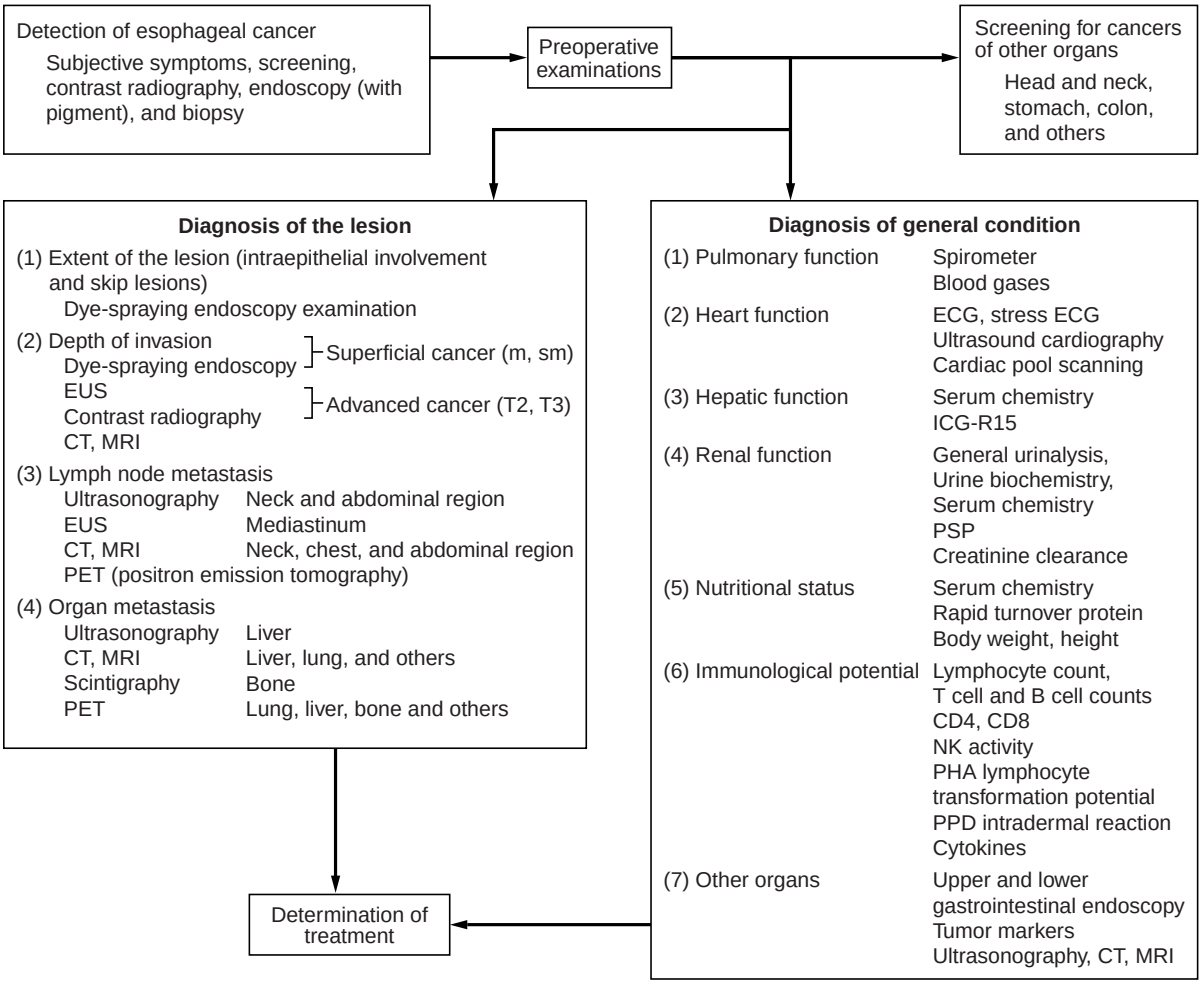

Fig. 1 Procedures for the diagnosis of esophageal cancer[8)]

mucosal epithelium to lamina propria mucosae), m3/sm1 (from lamina muscularis mucosae to surface of submucosa), or sm2/sm3 (middle layer of submucosa and deeper). If EMR is contraindicated for a given lesion, radical surgery is necessary. The difference in postoperative quality of life between the two treatments is significant and requires serious consideration. In Japan's aging society, merely treating patients with esophageal cancer is not sufficient; every effort must be made to use minimally invasive procedures whenever possible. In some cases, the selection of innovative treatment methods that enable a better quality-of-life (QOL) is also important.

Surgical treatments for esophageal cancer have improved, and the five-year survival rate of patients who undergo extended radical surgery with a three-field (neck, chest, and abdomen) lymphadenectomy through a thoracoabdominal incision now exceeds 60%. As esophageal cancer becomes curable, a trend toward minimum intervention has arisen; this trend has been welcomed by Japan's aging society. Endoscopic surgery is also becoming more popular.

Chemo and radiation therapies for esophageal cancer have been reviewed and trials (including molecular biology investigations) have been performed to establish the indications for combined therapy. The advent of EMR is noteworthy since this technique is

Table 1 Depth of Invasion, Vascular Invasion, and Lymph Node Metastasis of Esophageal Superficial Cancers

(%)

Depth of invasion	Number of cases	Vascular invasion	Lymph node metastasis
m1	17	0	0
m2	15	0	0
m3	11	6 (54.5)	1 (9.1)
sm1	13	8 (61.5)	2 (15.4)
sm2	20	16 (80.0)	8 (40.0)
sm3	34	28 (82.4)	15 (44.1)

positioned at the interface between medical and surgical therapies; a substantial difference exists between EMR and surgery from the standpoint of operational intervention and postoperative QOL.

The ideal diagnostic criteria used to determine the indications or contraindications of these various therapies are described below.

Indications for Surgery and Non-Surgical Treatments

To determine an appropriate course of treatment, the tumor's stage and the patient's general health must be identified (Fig. 1).

1. Tumor staging

1) Diagnosing depth of invasion

i) Superficial cancer

Endoscopy: Endoscopy examinations enable the invasion of superficial cancers to be identified. Endoscopy is particularly useful when combined with iodine staining for the identification of type 0-IIb m1/m2 lesions.[1] A summary of invasion depths is shown in Table 1. The accuracy rate of subclassification according to invasion depth is about 80%; when the cases are classified into m1/m2, m3/sm1, and sm2/sm3 lesions, the accuracy rate is more than 90%.[2,3] Clinically, diagnosis using this classification system is important for determining an appropriate treatment plan.

Endoscopic Ultrasonography (EUS): EUS can barely identify m2 tumors using a 20 MHz thin probe and can easily identify sm tumors. Two types of EUS systems, linear and radial, are used. A skilled investigator can attain an accuracy rate of 80% or higher.[4] The use of EUS is not widespread.

Contrast radiography: Typically, m3 lesions and deeper are discernible using contrast radiography, and the identification of sm cancers is relatively easy. The identification of m1 or m2 lesions is difficult unless a careful examination by a specialist is performed.[5]

ii) Advanced cancer

The diagnosis of T4 lesions (infiltration into periesophageal organs) is clinically critical.

CT and MRI: CT and MRI are useful tools for diagnosing aortic and tracheobronchial infiltrations and can be useful for differentiation between T3 (infiltration into esophageal adventitia) and T4 lesions. CT is widely used.

Bronchoscopy: Bronchoscopy is helpful for diagnosing tracheobronchial infiltration and indispensable for identifying T4 lesions. Bronchoscopic ultrasonography and intravascular endoscopic ultrasonography are also used at some facilities.

EUS: T3 and T4 lesions can be diagnosed using the 7.5 MHz probe. EUS is carried performed from the tracheobronchial or aortic side.

Contrast radiography: Contrast radiography is useful for diagnosing T4 lesions.

2) Diagnosis of lymph node metastasis

EUS, CT, and MRI are currently used to diagnose lymph node metastasis. The accuracy rate is approximately 80%.

3) Diagnosis of distant organ metastasis

Ultrasonography, CT, MRI, bone scintigraphy, PET, and other modalities are presently used to diagnose distant organ metastasis.

2. Patient's general health

(1) Heart, pulmonary, hepatic, renal, and central nerve function tests are performed

(2) Metabolic disorders, like diabetes, are identified

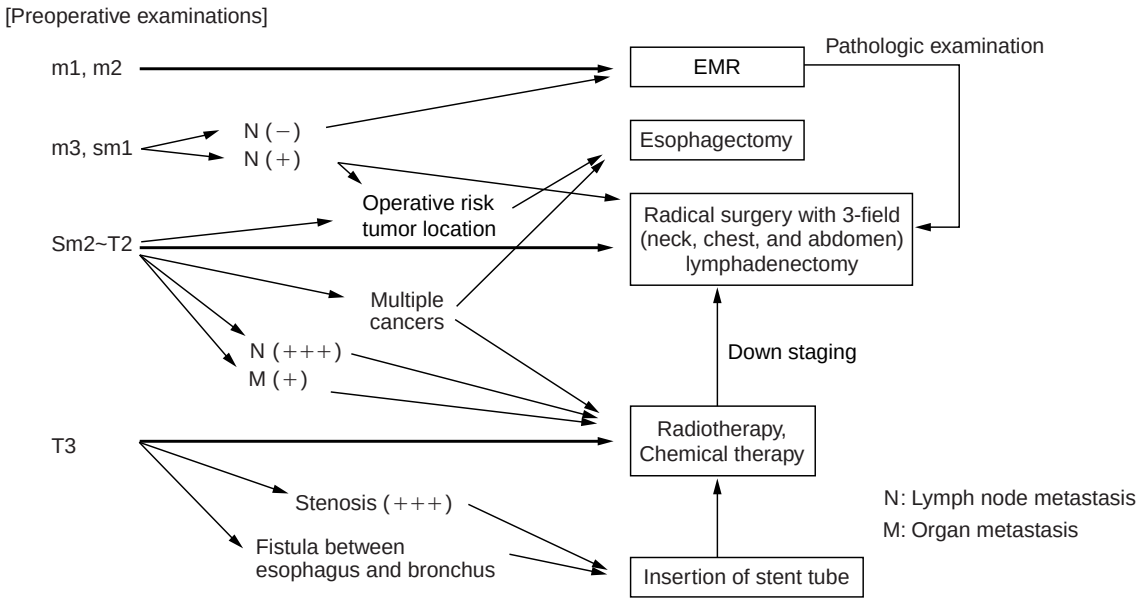

Fig. 2 Therapeutic strategy for esophageal cancer[8)]

3. Diagnosis of multiple cancers in other organs

The possible presence of head and neck cancer, gastric cancer, colon cancer, pulmonary cancer, and hepatic cancer is examined. In particular, a close relation has been found between head and neck cancer and esophageal cancer.

Treatment Strategy and Types of Treatment

1. Treatment strategy

As the number of radical resections of esophageal cancer increases, the pathology of this cancer is becoming clearer.

Esophageal cancers that are limited to within the mucosal epithelium (m1) or lamina propria mucosae (m2) seldom show lymph node metastases or vascular invasion. Lymph node metastases are found in 10–15% of cancers that infiltrate into the lamina muscularis mucosae (m3) or surface of the submucosa (sm1) and in 40% or more of cancers that infiltrate into the middle layer of the submucosa or deeper (sm2/sm3) (Table 1).

Based on the results of the various preoperative examinations described above, an appropriate treatment strategy is selected as shown in Fig. 2. Thus, preoperative examinations are essential to the process of selecting an appropriate treatment method.

a. EMR is performed[6)] for cancers whose depth of invasion is limited to m1 or m2.
b. EMR is performed for cancers with m3 or sm1 infiltration, that are not accompanied by enlarged lymph nodes, and that are technically operable. Radical surgery is selected as a treatment option after the histopathological findings of a resected specimen have been examined.

   Patients with suspicious lymph node metastases usually undergo radical surgery with a three-field (neck, chest, and abdomen) lymphadenectomy.
c. Radical surgery is performed for cancers with a staging of up to T2 and with sm2 or sm3 infiltration.

   Patients in poor general health and a high operative risk usually undergo a limiting esophagectomy. Patients with lesions located in the lower half of the lower intrathoracic esophagus (Lt) or abdominal esophagus

(Ea) and who have poor pulmonary function usually undergo a transhiatal esophagectomy or esophagectomy without thoracotomy. For elderly patients, an esophagectomy is performed using a left thoracoabdominal approach or a right thoracoabdominal approach, and a lymphadenectomy in the neck and superior mediastinum is not performed completely.

Patients with several suspicious lymph node metastases identified during the preoperative diagnosis may undergo preoperative chemotherapy.

Patients with remote organ metastases usually undergo chemo and radiation therapy.

For patients with multiple cancers in other organs, a treatment protocol consisting of a well-balanced combination of chemo and radiation therapy is implemented.

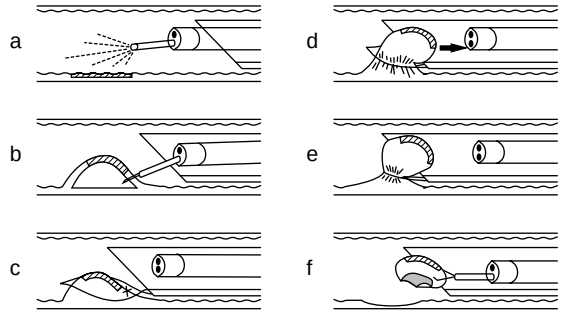

Fig. 3 EEMR-tube method
a. Iodine staining of the lesion. b. Lesion confirmation and injection of saline into the submucosal layer. c. Expand the snare on the lesion. d. Aspirate the mucosa into the tube using endoscopic suction. e. Squeeze the snare and resect the lesion using high-frequency current. f. Collect the mucosa containing the lesion for histopathological examination.

2. Types of treatment

1) Endoscopic mucosal resection (EMR)

The development and spread of EMR has changed the face of the treatment of esophageal cancer and at the same time has promoted a great advance in diagnostic methods toward early detection, especially the detection of mucosal cancer.

Whether EMR is indicated in a particular case is determined by two factors: the characteristics of the lesion and the required technique. The characteristics of the lesion include the depth of invasion and the presence of lymph node metastasis, while the technique refers to whether the lesion can be certainly and safely removed. With regard to the lesion characteristics, an invasion depth of m1–m2 (mucosal epithelium and lamina propria mucosae), a tumor diameter of less than 3 cm, a lesion measuring 2/3 or less of the esophageal circumference, and the presence of 3–4 lesions are considered to be good indications for EMR. Since radical surgery for esophageal cancer is highly invasive and greatly affects postoperative QOL, the indications for EMR have been expanded to include tumors with an invasion depth of m3 (lamina muscularis mucosae) or sm1 (surface of submucosa), a diameter of up to about 5 cm, and those that have spread over the entire circumference of the esophagus.

EMR techniques currently used include the EEMR-tube (endoscopic esophageal mucosal resection-tube) method (Fig. 3), the strip biopsy method, and the EMR-C method. We have used the EEMR-tube method in 497 cases or 736 lesions as of December 2000 (Table 2). We experienced various complications including esophageal perforation in 5 cases, arterial bleeding in 16 cases, and esophageal stenosis in 9 cases, but none of the patients required surgical treatment and no operative or in-hospital deaths occurred. Local recurrence and chronologically different multiple cancers were observed in 2.4% and 8.3% of the cases, respectively; most of these patients underwent a second endoscopic treatment. Efforts have been made to devise techniques that will enable the indications for EMR to be expanded to include tumors in difficult-to-operate regions, such as the entrance of the esophagus, the back of the exclusion toward the left main bronchus, and the esophagogastric junction. To date, more than 1000 patients have undergone EMR in Japan.

2) Radical surgery

Since almost half of the cases of submucosal

Table 2 Outcome of Endoscopic Esophageal Mucosal Resection

Total number of cases	497 cases		
Total number of lesions	736 lesions		
Esophageal cancer		409 cases	623 lesions
m1, m2		299	451
m3, sm1		94	106
sm2, sm3		16	17
Dysplasia		60 cases	78 lesions
Benign lesion		28 cases	35 lesions
Death due to surgical operation			0
Death during hospitalization			0
Complications	Esophageal perforation		5 cases (0.7)
	Subcutaneous emphysema		1 (0.2)
	Arterial bleeding		16 (2.2)
	Varicose bleeding		2 (0.3)
	Esophageal stenosis		9 (1.2)
Cases requiring surgery because of complications			0
Cases requiring surgery because of abnormal pathological findings			12
Local recurrence			15 lesions (2.4)
Chronologically different multiple cancers			34 cases (8.3)
Five-year survival rate			97.9%

(Keio Cancer Center, Tokai University; as of December 2000)

cancer are accompanied by lymph node metastasis, radical surgery with lymphadenectomy in three fields (neck, chest, and abdomen) must be performed in patients with lesions that infiltrate into the submucosa or deeper,[7] since the first lymph node metastasis from esophageal cancer can develop in a wide area, from neck to abdomen. Nowadays, radical surgery with an expanded lymphadenectomy can be safely performed, with the operative death rate as low as 1.5%. As the risk of undergoing this surgical procedure has stabilized, the outcome has improved, with the 5-year survival rate now exceeding 60%.

Some attempts have been made to perform this surgery using a thoracoscope and a laparoscope. Kawahara, Inoue, Kohno, Akaishi, Ozawa and other physicians have started to use this method in Japan, and the procedure is becoming well known. The technique reduces the effects of the procedure on breathing activity and is effective for preventing respiratory complications. Intrathoracic lymphadenectomies as well as thoracotomies can both be performed using a thoracoscope. Gastric tube reconstruction and intraabdominal lymphadenectomies can be performed using a laparoscope.

3) Chemo and Radiation Therapy

The main chemotherapeutic agents used for the treatment of esophageal cancer include cisplatin (CDDP), fluorouracil (5-FU), and calcium folinate (Leucovorin®). The chemotherapy regimen typically consists of 50–100 mg/m^2/day of CDDP for 1 day and 500–1,000 mg/m^2/day of 5-FU for 5 days; this regimen plus 10 mg/body of Leucovorin® and a regimen consisting of the continuous administration of low dosages of CDDP (10 mg/body) and 5-FU (250 mg/body) combined with concurrent radiation therapy (5 Gy/day × [5 days/week] × 2 weeks) are currently used. Recently 2 Gy/day × [5 days/week] × 6 weeks of irradiation for cervix, mediastinum and lesser curvature of

stomach combining with 2 cources of chemotherapy, 50 mg/m^2/day of CDDP for 1 day and 500 mg/m^2/day of 5-FU for 5 days are performed in some institutions in Japan.

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Prediction, Prevention and Treatment of Liver Cancer

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Abstract: Hepatitis virus infection has been reported to be responsible for liver cancer in over 90% of all cases (hepatitis C infection has been implicated in 80% and hepatitis B infection in 10%). Control of hepatitis virus infection has resulted in a steady reduction in the incidence of liver cancer. Following advances in the treatment methods of hepatitis C, the percentage of cases with hepatitis from whom hepatitis C virus can be eradicated has increased in recent years, from the previously reported 30% (recorded with interferon alone therapy) to over 50%. Eradication of this virus from the body in patients with liver cirrhosis has been shown to lead to remission of fibrosis, although this was previously impossible. Therefore, we clarified that the incidence of cancer can be reduced by this eradication method. What is now desired for the control of hepatitis C infection, which is one of the most common diseases in the Japanese people, is that the treatment that has been reported to be the most effective and has become the global standard, is approved at the earliest in Japan. It is also important that appropriate measures be taken in groups of individuals that are at increased risk of developing liver cancer.

Key words: HBV; HCV; HCC; Interferon; Ribavirin

Need to Control Hepatitis, a Very Common Disease in Japan

Following the discovery of hepatitis B virus in 1964, hepatitis viruses A and C were identified in 1972 and 1989, respectively. The roles of these viruses in Japan have been increasingly well clarified. That is, the pathophysiology of the three types of viral hepatitis has been elucidated, and appropriate treatment measures have been established.

In the past, it was a clinical practice at outpatient liver clinics in Japan to inform patients of changes in their serum GOT and GPT levels.

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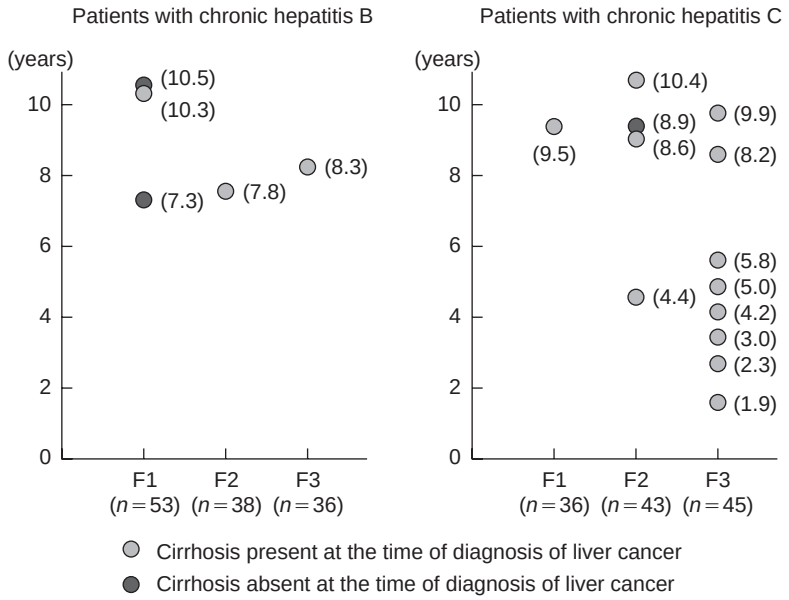

Fig. 1 Natural history of development of liver cancer in cases of hepatitis B and C (Reproduced with modifications from reference 1)

With further studies in this clinical field, it has now become possible to lay emphasis on informing the patients of the causes, give them an account of the natural course of their disease, and to discuss with them the measures to treat the disease.

Very High Incidence of Cancer among Virus Carriers

At present, out of the total of about 980,000 individuals who die annually in Japan, more than 30,000 are attributable to hepatocellular carcinoma. According to a recent survey conducted at University of Tokyo, hepatocellular carcinoma developed as a complication of hepatitis B in 11% of cases, and of hepatitis C in 83% of cases. This means that as many as 94% of all patients with hepatocellular carcinoma are hepatitis virus carriers, and that the ratio of the prevalence of HBV infection to that of HCV infection among patients with liver cancer has changed, with a significant increase in the prevalence of HCV infection among these patients.

Since 94% of all patients with liver cancer are virus carriers, it would seem reasonable to classify liver cancer by the causal virus type. The number of Japanese people infected with HBV and HCV is currently estimated to be 1.5–2 million each. The 8 : 1 ratio of the prevalence of HCV to that of HBV infection among patients with liver cancer clearly illustrates the close involvement of HCV in liver cancer.

To investigate the onset of liver cancer from chronic hepatitis, we followed the course of the patients who were definitively diagnosed to have chronic hepatitis (rather than cirrhosis) by liver biopsy (Fig. 1). Of the total patient population enrolled, 127 had hepatitis B and 124 were found to have hepatitis C. During the mean follow-up period of 6 years, hepatocellular carcinoma was diagnosed more frequently in the hepatitis C group (13 cases) than in the hepatitis B group (5 cases) (Fig. 1).[1)] When the numbers were converted into incidences per 100,000 population, the incidence of liver cancer per year was 647/100,000 in the chronic hepatitis B group, and 1,723/100,000 in the chronic hepatitis C group.

The incidence of liver cancer among non-hepatitis-virus-infected people (96%–97% of the total population) was estimated to be 1.7/100,000, taking into consideration various data. If this figure (1.7/100,000) were deemed, as it were, as the incidence of liver cancer in non-hepatitis-virus-infected cases, we may say that the incidence of liver cancer in patients with chronic hepatitis C is 1,000-fold higher than that in subjects without hepatitis virus infection. This difference is quite large, if one were to consider that the lung cancer risk ratio in smokers vs nonsmokers is about 10.

Latest Data on the Development of Liver Cancer in Chronic Hepatitis Cases

The percentage of patients with hepatitis who eventually developed liver cancer was compared among three groups of patients divided on the basis of the degree of fibrosis in the liver, as evaluated by liver biopsy (rated on a three-grade scale; mild [F1], moderate [F2] or severe [F3]). Thirty-six patients with hepatitis C were classified as having F1. Liver cancer developed in only one of these 36 patients during the subsequent 9.5-year follow-up period (Fig. 1). On the other hand, among the 45 patients with hepatitis C who were classified as having F3, cancer began to be seen as early as 1.9 years after the initial biopsy, with additional cases detected each year. The incidence of liver cancer in the F2 group was intermediate between that in the aforementioned two groups.

Let us use the step model to explain the course of development of liver cancer from chronic hepatitis. In this model, the group of patients starting from the third step reach the fifth step (onset of liver cancer), via the fourth step (cirrhosis), earlier than the group of patients starting from the first step. While this step model was practically valid for patients with hepatitis C, it was not for patients with hepatitis B. Of the 53 patients with hepatitis B in the first step (F1, mild fibrosis), three eventually developed liver cancer; however, only one of 36 patients in the third step (F3) developed cancer.

This is probably attributable to at least two different mechanisms of development of liver cancer in patients with chronic hepatitis B. One process is necrosis → inflammation → fibrosis (liver cirrhosis) → liver cancer. The other may be the development of liver cancer as an event independent of the underlying predisposing liver condition. Hepatitis C seldom follows the course of necrosis → inflammation → liver cancer in the absence of underlying fibrosis. We may say that in cases of hepatitis C, liver cancer develops only after a long course of development of fibrosis (cirrhosis), and not suddenly, in a normal liver.

When liver tissue surrounding the cancer-affected area of the liver was examined for the presence of cirrhosis in 13 patients who developed liver cancer secondary to hepatitis C, we noted that cirrhosis (F4) was present in the surrounding liver tissue in all but one of the cases (Fig. 1). We may therefore say that even in cases where the degree of fibrosis is initially mild (F1), cancer develops after the fibrosis progresses over a period of time to a severe grade (F1 → F2 → F3 → F4 → cancer), and not suddenly from the first step (F1). This probably explains the long period of 9.5 years that elapsed before the eventual development of liver cancer in one patient of hepatitis C in whom the degree of fibrosis was initially classified as F1.

In the hepatitis B group, although the number of cases was small ($n = 5$), the surrounding liver tissue showed no evidence of cirrhosis, but cancer developed in 2 cases (40%) (Fig. 1). These results indicate that the process of cancer development differs markedly between cases of hepatitis B and cases of hepatitis C. This assumption was endorsed by the findings in many cases examined subsequently.

How Can We Utilize the Above-Mentioned Information in Clinical Practice?

As stated above, the annual incidence of liver cancer in patients with chronic hepatitis C is 1,700/100,000, and that in patients with chronic hepatitis B is about 600/100,000. When the hepatitis C group was subdivided into F1, F2, and F3 groups according to the degree of liver fibrosis, the annual incidence of liver cancer per 100,000 was 457, 1,450 and 3,005 in the F1, F2 and F3 groups, respectively. Expressed as a percentage, the incidences are 0.45%, 1.5%, and 3%, respectively. If the average life expectancy of these patients, whose mean age was 40 years, were assumed to be 30 years, the probability of patients with F3 (severe chronic hepatitis) developing liver cancer during the rest of their life span would be 90% (3% $\times$ 30 years). On the other hand, the probability of patients with F1 (mild chronic hepatitis) developing liver cancer during the rest of their life would be only 13–14% (0.45% $\times$ 30 years); that is, slightly less than 90% of these patients would not develop liver cancer.

Indicators of liver function, such as the serum GOT and GPT levels, do not allow us to distinguish between patients who are likely and patients who are not likely to develop liver cancer. However, if the degree of liver fibrosis is evaluated by liver biopsy, it may be possible to predict whether a given patient with chronic hepatitis C is at a high risk or not of developing liver cancer during the remaining years of his/her life.

On the other hand, predicting the probability of development of liver cancer is difficult in patients with hepatitis B, even if the degree of fibrosis in the liver were evaluated by liver biopsy. Thus, although the incidence of cancer developing in cases of hepatitis is overwhelmingly higher in patients with hepatitis C than in those with hepatitis B, prediction of the probability of cancer development is more difficult in those with hepatitis B.

Concerning the development of liver cancer from cirrhosis (F4), data from all universities indicate that about 50–70% of patients with cirrhosis, secondary to either hepatitis B or C, develop cancer in 10 years.

Recently, the F classification (classification of fibrosis) was prepared within the framework of the new Inuyama classification (histological classification for liver biopsy). This classification, by which fibrosis is rated on a four-grade scale (F1: mild, F2: moderate, F3: severe, and F4: cirrhosis) is more suitable for the step-model mentioned above, that is, it is more appropriate for appreciating the clinical trend of the increasing number of patients with hepatitis C developing liver cancer.

Prevention of Cancer Development from Hepatitis C by Interferon Therapy

Considering the natural history of hepatitis C mentioned above, it should be possible to dramatically reduce the development of liver cancer from hepatitis C by eradication of the virus, prevention of the exacerbation of necrosis and inflammation and, if possible, suppression of liver fibrosis. In 1992, interferon (IFN) was authorized by the Japanese health authority for the treatment of hepatitis C. Since then, more than about 200,000 patients have been treated with this antiviral agent. It has been shown that in cases of hepatitis C, eradication of the virus by treatment with interferon reduces necrosis and inflammation and suppresses liver fibrosis, resulting in a decrease in the incidence of liver cancer in these cases.

Within the framework of the new 10-year counter-cancer program, we conducted a prospective-retrospective study of IFN therapy reducing the incidence of cancer.[2,3] With the cooperation of facilities nationwide, 2,890 cases were enrolled in this study, and 490 of these cases were followed up as untreated cases. The remaining 2,400 cases (the treated group) received IFN therapy, of which 33% (789 cases) showed CR (complete response), that is, the

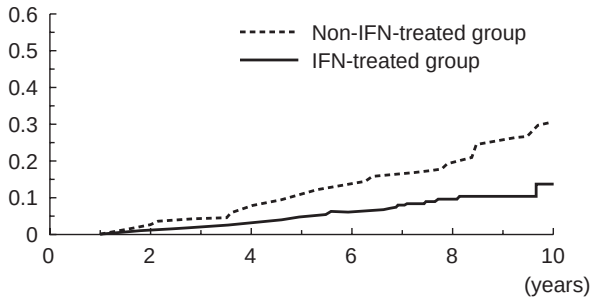

Fig. 2 Annual incidence of liver cancer (IFN-treated group and non-IFN-treated group)
(Reproduced with modifications from reference 2)

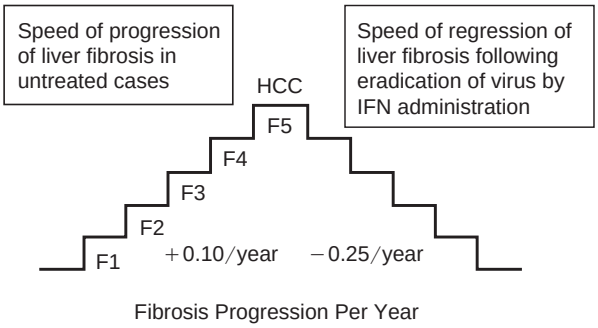

Fig. 3 Natural history of development of liver cancer in cases of hepatitis C
(Reproduced from reference 3)

virus was eradicated completely. Figure 2 shows the annual course of the incidence of cancer in the treated and untreated groups. The incidence of cancer in the treated group was only half of that in the untreated group.[2] Among the treated cases, those showing virus-free CR (accounting for 1/3 of all the treated cases) had a lower incidence of cancer (1/5 of the incidence in the non-treated group).

It is noteworthy that the incidence of cancer decreased to 1/5 also in those patients in whom the virus persisted but the serum transaminase levels normalized, although these cases accounted for only 11% of all treated patients.[2] This means that during the 4.3-year follow-up period, the incidence of liver cancer decreased dramatically in the group of patients in whom the serum transaminase levels normalized.

In the remaining 2/3 of all treated patients, the virus persisted. In this group, the liver functions remained abnormal. But, when these cases were subdivided into two groups (one in which the serum transaminase levels rose moderately to within twice the upper limit of the normal range, and a group in which the levels rose markedly during treatment to reach close to the pre-treatment levels), the incidence of liver cancer in the former group was 1/3 of that in the untreated group, and that in the latter group was approximately equal to the incidence in the untreated group. These results clearly indicate that normalization of the serum transaminase levels significantly suppressed the development of liver cancer in cases of hepatitis C, and that the decrease in the incidence of liver cancer was proportional to the degree of decrease in the transaminase levels.

F4 Fibrosis (Early-Stage Cirrhosis), Which Can Develop into Liver Cancer, Can also Be Attenuated by Virus Eradication

To investigate whether or not the above-mentioned suppression of liver cancer is attributable to suppression and/or alleviation of liver fibrosis, biopsy was conducted twice at an interval of about 3.7 years in 593 of the 2,890 cases (treated or untreated), to evaluate the changes in the degree of liver fibrosis.[3]

In the 106 untreated cases, the degree of progression of liver fibrosis ("fibrosis progression per year") was calculated. In the calculation method employed, the fibrosis progression per year was 2/4, i.e., +0.5, when the degree of fibrosis advanced from F1 to F3 during the 4-year period. When F3 improved to F1, the fibrosis progression per year was calculated to be −0.5. Calculation using this simple equation allows us to determine the speed of progression of liver fibrosis during the natural course of history of hepatitis.

In the untreated group, the fibrosis progression per year was calculated by the above method to be +0.1 (Fig. 3), that is, the fibrosis

Table 1 Annual Incidence of Liver Cancer (%) Classified According to the Degree of Liver Cirrhosis[a)]

	Hepatitis B	Hepatitis C	Platelet counts[b)]
F1	0.6%	0.45%	170,000
F2	0.4%	1.5%	150,000
F3	0.9%	3.0%	130,000

a) Converted from data shown in Fig. 1
b) This criterion does not apply to 15–20% of all cases. Below 100,000 in cases of cirrhosis (F4)

Table 2 Speed of Regression of Fibrosis Following Virus Eradication (Fibrosis Progression Per Year)

From F4 ($n=24$)	−0.28
From F3 ($n=45$)	−0.37
From F2 ($n=69$)	−0.28
From F1 ($n=42$)	−0.15

(Reproduced with modifications from reference 3)

Table 3 Standardized Mortality Rate

	Total death	Death from liver disease	Death unrelated to liver
Untreated group ($n=459$)	1.9	13.5	0.5
Treated group ($n=2,430$)	0.9	4.7	0.4
HCV eradicated ($n=817$)	0.4	0.8	0.3
HCV not eradicated ($n=1,613$)	1.1	6.5	0.4

(Reproduced from reference 4)

advanced (exacerbated) one level in 10 years. In the treated patients showing CR with virus eradication, the fibrosis progression per year was −0.28. It was thus shown for the first time that eradication of virus leads to about 2.8-fold faster alleviation of liver fibrosis than in cases where persistence of the virus is noted (Fig. 3).

Then, we investigated whether or not such dramatic alleviation of fibrosis takes place to a similar degree in all cases, irrespective of differences in the pre-treatment stage of fibrosis rated according to the F classification. We found that the fibrosis progression per year was −0.28 even when the starting stage of fibrosis was F4. Thus, this parameter was approximately the same, regardless of the initial fibrosis grade (Table 2). These results indicate that if the virus can be eradicated, fibrosis can be alleviated even in cases with cirrhosis (F4), and that even in F4 cases, the alleviation of fibrosis can proceed at a speed comparable to that seen in cases with less severe fibrosis (Table 2).[3)] This study thus succeeded in demonstrating, for the first time, the speed of fibrosis during the natural course of history of hepatitis C, and that even liver cirrhosis can be alleviated. In treated patients in whom the virus could not be eradicated, the fibrosis progression per year was +0.02 during the follow-up period, indicating that the progression of fibrosis could be stopped in these cases also, although the effect was probably only transient.

These results exhibit close similarity to the findings in the 124 patients with chronic hepatitis C mentioned above, in that they indicate that the probability of liver cancer developing in cases of hepatitis C becomes higher as the degree of fibrosis becomes more severe. This suggests that success in suppressing the progression of fibrosis or promoting the alleviation of fibrosis would basically reflect as success in suppressing the development of liver cancer in cases of hepatitis C.[3)]

Anti-HCV Therapy Reduces the Total Death Rate

We believe that the incidence of liver cancer in cases of hepatitis C can be clearly reduced by treatment.[2,3)] What impact will this have on the total death rate from all causes, including cardiovascular and other causes of death? We demonstrated for the first time that IFN therapy can also reduce the total death rate (Table 3).[4)]

We investigated the death rate and the cause of death in both the IFN-treated and non-IFN-treated groups. Standardized mortality rates (SMRs) were obtained by matching the age and male-to-female ratio of our population to those of the total Japanese population reported in Japanese population statistics.

The SMR for the non-IFN-treated patients with chronic hepatitis C was 1.9, while that for the IFN-treated patients was 0.9. The rate decreased to 0.4 (a level lower than that for the general population) in the group of patients in whom the virus had been eradicated (Table 3).

For diseases other than chronic hepatitis C, there are few reports that demonstrate that the total death rate of patients with a given disease can be reduced by treatment of the disease. Our study, however, showed that the total death rate of patients with chronic hepatitis C could be reduced by treatment. It also confirmed that a high percentage of patients with chronic hepatitis C die of liver cancer. There is therefore urgent need for the development of more effective means of treating this disease.

Perspectives for the Development of New Methods for the Eradication of Hepatitis C Virus

Currently, the standard regimen employed internationally for the treatment of hepatitis C is combined IFN and ribavirin therapy. The above-mentioned decreases in the incidence of liver cancer and total death rate in the treated cases refer to the results of administration of IFN alone for the treatment of hepatitis C (conventionally used in Japan).

Let us see the current status of combined drug therapy for hepatitis C. On December 7 last year, combined IFN and ribavirin therapy was authorized for the treatment of viral hepatitis under the National Health Insurance (NHI) system in Japan. Figure 4 compares the results of the various treatment methods for hepatitis C employed in Japan and other countries in patients with high blood levels of Ib type HCV (a type of HCV that is known to be difficult to eradicate).

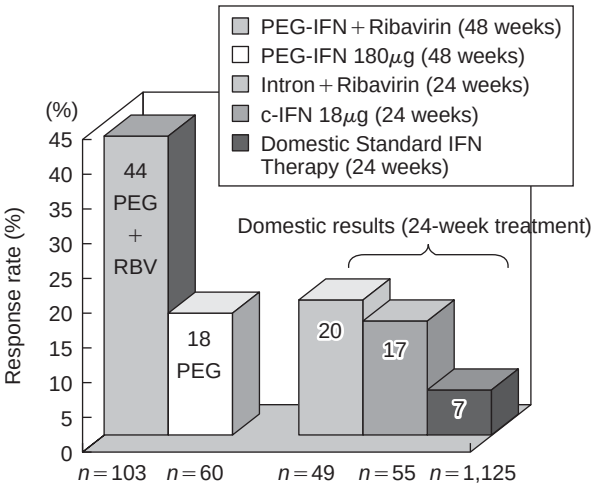

Fig 4 Sustained virological response or "eradication" of patients with high levels of Ib type HCV to treatment

The percentage of patients in whom the virus could be eradicated was only 7% in the group of patients treated with IFN alone (the therapy conventionally used in Japan). Among the patients treated by combined IFN and ribavirin therapy also, which was recently authorized for the treatment of viral hepatitis under the NHI in Japan, the percentage of cases in whom the virus could be eradicated was not satisfactorily high (about 20%), even though it was higher than that in the group treated with IFN alone. At present, combined PEG-IFN (polyethylene glycol-IFN) and ribavirin therapy is employed as a standard regimen all over the world. In this regimen, PEG-IFN is administered only once in a week. The percentage of cases in whom the virus was eradicated after 48 weeks of combined PEG-IFN and ribavirin therapy was as high as about 46%, more than double that in the group of patients administered ordinary IFN in combination with ribavirin. The incidence of adverse reactions, such as fever, was also low with the use of this new regimen, which has already been authorized for the treatment of hepatitis C in Europe and the United States. It would be desirable if this regi-

men were authorized as soon as possible in Japan as well, since this country has a large number of patients at high risk for liver cancer (patients with F3 or F4 hepatitis).

Conclusion: Desirable Improvements in Antiviral Therapy in Japan

1. Combined PEG-IFN and ribavirin therapy, a regimen which is becoming a global standard, should be authorized as soon as possible in Japan.
2. Even though Japanese investigators (including our own group) have reported evidence highlighting the increased risk (5–7%) of liver cancer in patients with F4 liver fibrosis (cirrhosis), antiviral therapy for F4 hepatitis is not authorized under the NHI in Japan. In foreign countries, active clinical intervention to treat F4 has been employed based on data for high-risk groups reported from Japan.
3. Economically efficient antiviral therapy, taking into account the patients' QOL, should be provided to Japanese patients. In Japan, IFN is generally expensive. However, the current policy of the NHI in authorizing the use of IFN does not adequately consider the significantly increased risk of liver cancer in cases of viral hepatitis. That is, relatively low-risk F1 and F2 cases are covered by insurance, while high-risk F4 cases are not. It would therefore, in conclusion, be desirable to provide low-cost IFN efficiently, review the indications of this therapy, and emphasize the value of treating F3 and F4 cases who are at markedly high risk of developing liver cancer.

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Parents with Childrearing Anxieties

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Abstract: With the increased number of nuclear families in recent years and diminished community ties, mothers have become increasingly socially isolated. Lacking the support and cooperation of their spouses and faced with the problems of raising a difficult child, mothers, especially full-time mothers, are beset by feelings of isolation and a strong sense of obstruction. They gradually begin to feel burdened by childrearing responsibilities that may develop into anxieties. The physician must encourage the mother to make prenatal visits and to discuss the importance of breastfeeding and mother-child behavioral attachments prior to the birth of the infant. Following the birth of the child, the physician must understand and be aware of the mother's anxieties regarding her childrearing responsibilities and he must provide counseling with understanding, sympathy and warmth during her regular outpatient health examinations. It is important for the physician to maintain an attitude of constant support. The mother should be actively encouraged to participate in specific activities such as childrearing group meetings and to exchange information in such support activities. The physician will be expected to know about and to utilize the community childrearing support network.

Key words: Childrearing anxieties; Sukoyaka Family 21; Childrearing support; Postpartum mental health; Childrearing support network

Introduction

One of the four principle concepts promoted and envisioned by the Ministry of Health, Labour, and Welfare in its report on "The Mother-Child Health Promotion Campaign for the 21st Century" (Sukoyaka Family 21) is to promote the untroubled mental health development of children and to alleviate the childrearing anxieties of the mother.[1)] Cultivating an awareness of the existing problems, defining the orientation and specific measures that should be adopted are addressed in this report.

Promoting the mental health of the parent and child is one means of preventing potential mental health problems that may occur during the adolescent stage of a child's development. Special emphasis has also been placed on the

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need to cope with the parent's anxieties related to childrearing responsibilities. Sukoyaka Family 21 is an exceedingly important countermeasure that will establish comprehensive and nationwide measures aimed at alleviating the anxieties of the mother about pregnancy, birth, childrearing responsibilities, and thereby allow her to enjoy her childrearing activities and to ensure the sound mental development of her child.

The physical growth and mental health development of a child is affected when the mother suffers from childrearing anxieties during the infancy period. Physicians, especially pediatricians, are greatly concerned about mothers suffering from childrearing anxieties, and they are responsible for actively supporting them to ensure the sound physical and mental health of the next generation.

This paper focuses on the important role of physicians, especially pediatricians, who are active at the forefront of infant health, and the approach that is adopted to help mothers suffering from childrearing anxieties.

Childrearing Anxieties Observed at the Pediatric Outpatient Clinic

Based on the idea that there were many young and first-time mothers suffering from childrearing anxieties, the author began holding monthly class sessions on child-raising activities at his pediatric clinic from about eight years ago. Some of the topics that are discussed are the basic mental attitude that should be adopted by the mother, techniques, helpful hints and suggestions about childrearing activities. At the beginning of each class session, each mother is asked to candidly describe her thoughts and feelings about childrearing. Some mothers have cried and confessed to forcibly shutting the mouths of their crying infants out of irritation, choking the infant's neck, and other abusive behavior. The large number of mothers who suffer from child-raising anxieties is shocking.

To further ascertain and corroborate the existing conditions, a survey on the mothers who had participated in the childrearing class sessions was conducted in 1996.[2)] Each mother was asked to fill out a questionnaire, and the findings that were obtained surpassed expectations. Of the 66 valid responses that were received (a response ratio of 51 percent), 16 percent of the respondents stated that they had or continue to have strong anxieties about their childrearing responsibilities; 36 percent stated that they became periodically anxious; and 44 percent said that they almost never experienced anxieties about their childrearing responsibilities. As these findings show, the majority of the respondents had experienced childrearing anxieties to a greater or lesser degree.

A survey was conducted on 13,084 mothers with four-month old infants who underwent a health examination from April to December 1998 in Fukuoka City. In response to the question, "Is childrearing enjoyable?", 78 percent responded "yes", 1 percent responded "no", and 21 percent responded as "neither". In a survey of mothers taken during medical checkups, there was an 8 percent decrease in the ratio of mothers who responded that childrearing was enjoyable as their infants reached 1.6 years and 3 years of age. But in general group surveys, the ratio of mothers who responded that "childrearing was enjoyable" was rather high. Therefore, informing a pregnant woman prior to the birth of her child that "childrearing is basically an enjoyable task" is beneficial.

It should be cautioned, however, that the onset ratio of childrearing anxieties differed greatly according to the group characteristics of the mothers at the time of the survey. Some survey findings show that the majority of the mothers experience childrearing anxieties. But, an objective and appropriate figure is about 20 to 25 percent for mothers with children up to the age of three years.

Typical examples of childrearing anxieties described by mothers who participated in childrearing class supervised by the author have

been introduced below.

"I'm unable to prepare three daily meals satisfactorily and my child won't eat. Since my child is so physically small, I try to force him to eat, but he refuses to eat obediently. It inevitably ends up in a vicious daily cycle of spanking and crying".

"I had no one to whom I could turn for advice and I was often depressed. I read childrearing books over and over, but none of the examples that were given fit my situation and I was beyond myself. My child cried so often and I was so worried that she was ill".

These are two candid descriptions that aptly show the actual state of childrearing anxiety.

In answer to the question, "Have you ever become physically violent toward your child?", 43 percent of the mothers responded affirmatively. The physical violence consisted mainly of slapping the child's hands or spanking. However, there were some serious cases of face slapping and other more abusive behavior. Of these more serious cases, 59 percent of the mothers responded that "they were trying to discipline their children", and 32 percent or one-third of the mothers responded that "they had lost emotional control".

Cause of Childrearing Anxieties

Before examining countermeasures to address childrearing anxieties, the underlying causes will be discussed as to why this phenomenon is increasing and why it is seen as a social problem.[4)]

The increased number of nuclear families in recent years and diminished community ties that have socially isolated the mother have been pinpointed as the cause of childrearing anxieties.

The natural outcome is that the full-time mother in particular, is beset by feelings of isolation, a strong sense of obstruction, and gradual feelings of being burdened by childrearing responsibilities due to poor cooperation between couples with regard to the childrearing task, especially in the case of difficult children.

In addition, in many cases, the mother has few friends, had gotten married and given birth with minimal real experience in nurturing infants and with very limited learning about being a mother. Therefore, she has minimal confidence about raising a child and she is very anxious. When her mother's assistance during the first month after the birth of the child ends, her anxiety increases, her confidence completely disappears, and she becomes overly nervous about trivial matters such as difficulty in breastfeeding, the infant's refusal to eat during the weaning stage, and the inability to sleep at night due to the infant's crying throughout the night. The mother becomes worn out by childrearing responsibilities which are compounded by spousal disagreements and eventually begins to blame the infant for her troubles (if only this child had not been born). This develops into frustration that leads to child abuse and in some serious cases, the mother begins to harbor feelings of murderous intent toward her child. There is a need to confront the reality of mothers who are forced into abusing their children.

The Infant Health Committee of the Fukuoka City Medical Association has conducted health examinations for infants based on the approach adopted by the Fukuoka City Medical Association. The data that has been collected thus far has been compiled into a database at the Health Care Information Department of Kyushu University, and more than 100,000 cases have been recorded since its start in 1987. In the observation survey mentioned earlier, the mother's feelings about childrearing responsibilities were surveyed and notable findings were obtained.[5)]

The findings obtained from a survey of 13,914 mothers under the age of 49 during a one-month infant health check-up, showed that 40 percent of new mothers responded that they were worried, 37 percent admitted to emotional fatigue, 51 percent admitted to physical

fatigue, and 50 percent responded that they lacked confidence.

Childrearing anxieties experienced by first-time mothers were clearly indicated statistically. As shown in Fig. 1, these anxieties distinctly tended to decrease with the second and third child. Thus, childrearing anxieties improved with the increased experience of the mother.

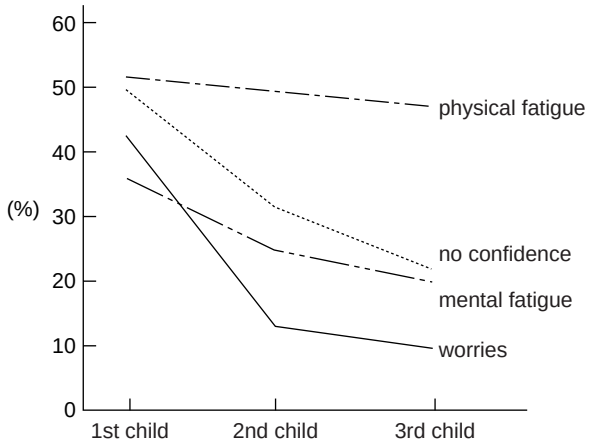

Fig. 1 Emotional state of the mother about childrearing at the first month health examination

Furthermore, among the many factors that were studied in this survey, it was found that the primary factors that contributed to childrearing anxieties, which developed within the first month following the birth of the infant and were statistically corroborated, were first-time births by women over the age of 30, mothers who had male infants rather than female infants, mothers who did not breastfeed their infants, infants who did not breastfeed well, infants who did not gaze at their mother's faces, the occurrence of an accident, and others. Thus, if these primary factors are recognized, measures to prevent childrearing anxieties can be taken during the health examinations.

How to Deal with Childrearing Anxieties

How should physicians treat the onset of childrearing anxieties? Firstly, prior to the birth of the child, there is a need to discuss the joys of childrearing and the miracle of giving birth with the mother, especially in the case of unplanned pregnancies where the mother's

Table 1 Advice for Mothers on How to Maintain Mental Health after Delivery[6)]

1. Try to give birth under conditions that you find satisfactory based on thorough conversations with your husband and midwife during your pregnancy.
2. Get ample physical and mental rest following delivery.
3. Don't hesitate to ask questions about concerns related to your baby (such as jaundice) and keep asking questions until you fully understand the explanations.
4. If you feel that you are suffering from the maternity blues, tell your husband and family members. It is very important that there is someone nearby to watch your condition.
5. It is not your fault, if your baby is delivered through caesarean section or a forceps operation. It is important that you get adequate rest and try to regain your strength.
6. Don't overexert yourself—your baby will grow and develop at its own pace. Relax and accept the help and assistance of your husband and other persons around you.
7. All mothers commonly worry about whether they have sufficient breast milk. If your baby gains weight satisfactorily, there is nothing to worry about.
8. Many new mothers become anxious when their parent or home helper is no longer able to help out. Seek the advice of other mothers who can share their experiences with you.
9. There is no fixed child care manual book available. Do not allow yourself to be confused by other opinions, and do what you think is best because it is about your child.
10. Be strong and confident about yourself, and think positively when you run into problems. Don't hesitate to seek assistance when in need. The fact that you're able to seek help when you need it is proof that you're being strong and confident!

emotional preparation has been inadequate. Simultaneously, it is important to inform the mother about the significance of engaging in loving behavior such as breastfeeding between the mother and child, which contributes positively to the emotional development of the child in the future, and about maternity blues, postpartum depression, and other emotional disorders that are seen after birth. Table 1 lists the advice given by Dr. Yoshida aimed at maintaining the mother's mental health following the birth of the infant.[6)]

Thus, continuity between prenatal and postpartum care is needed. To ensure this continuity, the obstetrician should introduce the pediatrician and inform the mother of the need for prenatal visits. The involvement of the physician with the mother to prevent childrearing anxieties is important.

It is fundamentally important that the physician maintains a supportive mindset and shows consideration and understanding of a mother's childrearing anxieties during outpatient examinations and health check-ups. Specific examples of physician support for mothers experiencing childrearing anxieties are given below.

1. Give the mother confidence

Generally, mothers suffering greatly from childrearing anxieties have very little self-confidence. Firstly, it is important to praise the mother by telling her that she's doing a good job. Secondly, encourage her to enjoy childrearing activities, relax and discourage any feelings about having to raise her child according to a set manual. Warm words of encouragement from the physician will give the mother courage and ease whatever burden she may be feeling about her childrearing responsibilities. She will see the physician as a good source of advice; and to gain her trust and confidence, the physician should always show a smiling demeanor irrespective of how busy he is, and adopt a sympathetic listening manner that will encourage the mother to communicate her anxieties candidly. The physician must speak kindly and gratify her need for warmth and understanding.

2. Be aware about the serious effect of a physician's statement

The physician should be careful not to cause the mother unnecessary anxiety when communicating measures to rectify symptoms that are not clearly abnormal such as slightly low weight or height of the infant or slightly slow development. It is important that physicians, nurses, public health nurses, and psychotherapists are aware of the serious effect that their statements have on mothers. For example, "the child shows slow development" or "there is a problem", and other negative statements that cause a mother with childrearing anxieties further worries should be avoided.

When a specialist is introduced for a secondary detailed examination, informing the parent about clearly known diagnostic names such as cerebral palsy or lagging mental development should be avoided. The physician should inform the parent that a specialist is being introduced because "I'm slightly concerned about x-symptoms and I want to have a specialist take a look at the child to be on the safe side". The parent should be given hope and told that generally the brain of a child grows in parallel with the child's physical development.

3. When confronted by a mother with childrearing anxieties

Occasionally, mothers suffering from childrearing anxieties, especially mothers with a first child, will visit the clinic to seek advice about the inability to produce sufficient breast milk, the infant's refusal to drink milk, depression, the lack of concentration, irritation, and other worries while confessing to a lack of confidence about childrearing activities or the inability to feel loving toward the infant. During the breastfeeding period, particularly the first four months following the birth of the infant, medical checkups must take maternity blues into consideration. Therefore, it is important to

place the focus of attention on the mother's attitude rather than solely on the infant.

The physician must not tell the mother that "she must do this or that", "be strong", "you're a mother now, so you've got to cheer up and be strong", and other words of encouragement that may sound lecturing. Rather, the physician must adopt a sympathetic attitude that communicates his willingness to listen to the mother's point of view. The physician should maintain a supportive and sympathetic attitude to minor complaints by the mother such as "my child often catches cold", "my child develops rashes easily", and "my child doesn't eat well". Simultaneously, he should help foster the mother's attachment to her child by encouraging maternal behavior. The aim is to enable her to love her child and to feel happy about having given birth.

4. Childrearing is a shared task between both genders

In view of the tendency for mothers to become emotionally isolated due to diminished community ties and the growing advent of the nuclear family, communication is vital and necessary to gain the understanding and cooperation of the spouse regarding childrearing activities. Fundamentally, the role of the father is not simply to support the mother in her childrearing activities, but to realize that the childrearing task is a shared responsibility of both genders. No matter how tired or exhausted the father may be after returning home from work, it should be emphasized that the concerns faced by the mother in her childrearing activities must be addressed jointly.[8] Qualitative rather than quantitative participation by the father in childrearing activities is important. A mother's childrearing anxieties are considerably reduced when her husband's participation is highly valued by the mother irrespective of how late his return home from work is on a daily basis.

5. Role of the community

According to the data obtained from 1,164 cases of infant medical examinations surveyed using the approach adopted by the Fukuoka City Medical Association mentioned earlier, the ratio of employed mothers suffering from childrearing anxieties was clearly lower than the ratio of full-time homemakers suffering from childrearing anxieties.[9] Generally, many stay-at-home mothers suffer from feelings of isolation and childrearing anxieties. Therefore, it is important for the mothers to cultivate friendships with neighbors whom they can seek advice or support. Concrete information about support activities or childrearing circles should be provided and they should be actively encouraged to participate. If the mother is unable to obtain such support, it is important that she is informed by the physician that his support is always available and to seek his advice rather than to worry about childrearing issues in isolation. This will help alleviate the emotional burdens of a mother suffering from childrearing anxieties.

Other countermeasures include putting the child temporarily in a day care center through the local welfare office or to utilize pediatric hospitalization services in the case of a sick infant. This will temporarily relieve the mother from her childrearing responsibilities. Therefore, the pediatrician who is at the forefront mother-infant care is required to have adequate knowledge and information about a childrearing support network based on community resources such as public health centers, day care centers, Child Consultation Center, women's centers, family support centers, and Child 110.

6. Questions to mothers troubled by childrearing concerns

There is a need for the physician to sympathetically ask a mother suspected of suffering from childrearing anxieties such questions as "What are you presently worried about?", "What time do you nurse your child?", "Does he/she cry constantly throughout the night?",

"Are you able to get enough sleep?", "Are you able to make time for yourself?", "Do you have a babysitter?", "Does your husband come home late?", "How does he help you?".[10)]

The physician should also encourage the mother to ask questions during medical and health examinations. It is important that he does not immediately refute the mother's complaints despite their medical irrelevancy and that he adopts a sincere attitude and willingness to listen to the mother. If the physician perceives that the mother does not have someone with whom she can seek help or advice, he should inform her that she should be free to consult him with whatever worries or concerns that she may have or to tell her that since he fully supports her position as a mother, her worries about childrearing should not be borne alone. It is important that the physician provide added encouragement such as "worries about childrearing matters don't last forever and your worries will be over in no time" to mothers with childrearing anxieties.

Mental Illnesses and the Pediatrician

Several issues about childrearing anxieties and other mental illnesses that are encountered by the pediatrician are briefly introduced here.[4)] Generally, it is customary for experienced physicians in clinical pediatrics, to quickly diagnose the disease, treat and cure it as in the case of infectious diseases. Thus, when the pediatrician encounters mental illnesses, they are susceptible to making the following mistakes. Firstly, (1) impatience or the lack of tolerance when the illness is not cured quickly, (2) the tendency to seek cause and effect solutions as is typically done in infectious disease models in pediatrics, especially in the case of mother related illnesses where the pattern is to question the responsibility of the mother, and lastly, (3) the pediatrician will tend to overwork the solution.[11)]

These tendencies of the pediatrician are highly unsuited to coping with mental illnesses and are adverse. Thus, in order for pediatricians to actively treat childrearing anxieties and other mental illnesses, they must be adequately aware of these negative tendencies. The solution is not for the pediatrician to cure childrearing anxieties through personal guidance, but fundamentally, it is important for him to resolutely fulfill the role of a confidant, to patiently listen carefully and sympathetically to what the mother is saying, and to address the illness together with the mother.

In the past, the mental illness of mothers and children stemming from childrearing anxieties was not covered in medical textbooks and subsequently, the general pediatrician was inexperienced in treating these illness. But presently, interest in this mental illness has risen among pediatricians throughout the country, and research and study in this field have flourished. As a result, childrearing support activities centered on the pediatrician have been markedly and actively pursued. One of the elements that should characterize outpatient pediatric services in the 21st century, is the advice or expertise that is given in community maternal and child health care.

Conclusion

In an age when young mothers have limited experience in motherhood and must learn about the task of childrearing, the basic means of coping with childrearing anxieties over a long-term period is to organize community childrearing learning centers in order to help women during their pre-teen and teenage years to learn about childrearing responsibilities and tasks through the shared personal experiences of others. It is also desirable that a public educational program about child rearing is organized for young parents. Simultaneously, field and study trips to health centers and maternity clinics and hospitals by junior high and high schools aimed as strengthening childrearing education is also another effective means of preventing future cases of childrearing anxieties. It is vitally important that young people

are educated about the joys of birth and the enjoyment of raising children during their adolescence. Outpatient pediatric services must actively promote the need to carry out such measures in their respective communities.

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