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Practice and Problems of Interferon Therapy
—Advanced renal cell carcinoma—

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Abstract: IFN-α monotherapy, with response rates ranging from 10 to 20%, is a standard choice of immunotherapy for advanced renal cell carcinoma (RCC). In this review article, the clinical efficacy and feasibility of IFN-α or IFN-α based regimens are summarized. Subcutaneous or intramuscular doses of 3 to 5 million units/day or three times weekly for IFN-α are often used in Japan. Concerning the clinical results with IFN monotherapy, IFN-γ is not superior to IFN-α. To date IFN-α-based regimens involving combination treatments with IFN-α plus IFN-γ, retinoic acid, 5FU or vinblastine have been tried. The overall response rates for each of the treatments have been almost similar to, or sometimes even lower than, those for IFN-α monotherapy. A protocol with IFN-α plus IL-2 and 5FU showed better results in some recent trials, in terms of response rate and long-term survival duration. Patients showing a complete response (CR) to high dose IL-2 regimen tend to survive longer than patients showing CR with IFN-α. However, we must beware of the level of toxicity that comes with the high dose of IL-2. Inravenous doses of more than 2.1 million units/day for IL-2 are not currently covered by health insurance in Japan. Further investigation of clinical results of the combination treatment with IFN-α plus low dose of IL-2, with or without 5FU in randomized studies, remains a priority in research towards improving the outcome of patients with advanced RCC.

Key words: Advanced renal cell carcinoma; IFN-α; IFN-γ; IFN-α combination therapy

Introduction

Renal cell carcinoma is resistant to chemotherapy and radiotherapy and its prognosis is poor in patients with metastasis. The disease is mainly treated with surgery or immune therapy using interferon (IFN) or interleukin 2 (IL-2).

IFN consists of a group of antiviral proteins secreted from cells of vertebrates in response to various inducing agents. It inhibits cell growth and modulates immune responses. IFN has been used alone or in combination with

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Table 1 IFN Therapy for Renal Cancer

A. Efficacy rate by the type of IFN

IFN	Number of institutions	Number of patients	Response rate		
			CR	PR	Total (%)
IFN-α					
natural leukocytes	6	141	6	20	26 (18)
natural lymphoblastoid	11	398	4	57	61 (15)
recombinant	16	573	10	73	83 (14)
IFN-γ	6	121	1	10	11 (9)

CR: complete response, PR: partial response
(Horoszewicz, J.Js., *et al*.: *J Urol* 1989[4] modified)

B. Titer and efficacy rate of IFN

Daily dose (MU)	Number of institutions	Number of patients	Response rate (%)
<5	6	97	6
5–10	3	208	13
10–20	5	131	19
>20	9	332	12

(Wirth, M.P.: *Urol Clin North Am* 1993[3] modified)

multiple drugs.

IFN-α

IFN is known to stimulate immunity by increasing NK activity, enhancing the expression of MHC class I antigen, and increasing the activities of macrophages and K cells. However, it has not been determined whether the effect of IFN on renal cell carcinoma results from such immunoactivating effects or its inhibitory effect on cell growth.

Quesada[1] and Marushige *et al.*[2] reported that IFN therapy for advanced renal cell carcinoma produced a response rate of 36.5% and 16.7%, respectively. Since then, IFN therapy has been examined in many clinical studies as the mainstream treatment for renal cell carcinoma. Natural-type interferon (nIFN), such as Sumiferon® (lymphoblastoid-IFN) and OIF® (leukocyte-IFN), and recombinant interferon (rIFN), such as Canferon® (IFN-α2a) and Intron A® (IFN-α2b), are generally used in Japan. Although the response rate of IFN depends on its type, target groups, and therapeutic regimens, it is generally considered to range from 12 to 19% based on the results from a population of more than 1,000 patients (Table 1).[3,4]

1. Dosage and administration method

nIFN is intramuscularly or subcutaneously administered at 3,000,000 to 5,000,000 IU/day (3 to 5 MU/day) or 5 to 10 MU/day every day or thrice weekly. rIFN is intramuscularly administered at 3 to 10 MU/day or 6–18 MU/day every day or thrice weekly. IFN is generally administered at 3 to 5 MU/day for a long time in Japan. Increasing the dosage above 5 MU results in almost no improvement in response (Table 1). For the administration route of IFN, subcutaneous, intramuscular, and intravenous administration produced a response rate of 14, 18, and 8%, respectively. This indicates the superiority of the subcutaneous and intramuscular routes to the intravenous route.[4] Since the clinical effect of IFN is often observed during

the initial 3 months of treatment, the administration of IFN is discontinued at 3 months in patients in whom the disease progresses in spite of IFN therapy.

2. Indications of IFN therapy and prognostic factors

A recently published prospective randomized comparative study showed that IFN-α prolonged the survival period: 167 patients with advanced renal cell carcinoma treated with IFN (10 MU, thrice weekly for 12 weeks) showed an increase in median survival period by 2.5 months as compared with 168 control patients treated with medroxyprogesterone hydrochloride (300 mg/day for 12 weeks continuously).[5] Another study showed an increase in the survival period by about 30 weeks in patients treated with vinblastine (VBL) + IFN as compared with those treated only with VBL.[6] However, there is a report that IFN did not prolong survival as compared with progesterone.[7] Thus, the effect of IFN in prolonging survival has not been established. A recent study reported that IFN as used for the adjuvant therapy after radical nephrectomy had no effect on the survival period or prevention of recurrence.[8]

Previous clinical findings indicate that beneficial effects from IFN therapy can be expected in patients to whom any of the following factors apply: (1) pulmonary or lymph node metastasis, (2) removal of the primary lesion, (3) good performance status (PS), (4) no marked increase in CRP, ESR, or IAP, (5) no spindle cell cancer component, and (6) a long interval from nephrectomy to recurrence.

Based on the examination of 670 patients with advanced renal cell carcinoma, Motzer *et al.*[9] reported that negative factors for the survival period included reduced PS, increased serum LDH, hypercalcemia, anemia, and no history of nephrectomy, and that the prognosis for patients could be classified according to the number of applicable factors. Therefore, the outcomes of IFN therapy can be guided to some degree by avoiding patients with any of these negative factors and administering IFN in patients with pulmonary or lymph node metastasis.

3. Adverse reactions

Most patients treated with IFN complain of influenza-like symptoms (fever, chill, myalgia, and malaise). Other adverse reactions that may often occur include headaches, anorexia, leukopenia, thrombocytopenia, and hepatopathy. However, all these adverse reactions are resolved by withdrawing IFN. Attention should be paid to rare adverse reactions, such as depression symptoms, interstitial hepatitis, transient visual loss, and epileptic seizure.[4,5,10] Combination with Sho-saiko-to is contraindicated because it may induce interstitial pneumonia.

Gene Recombinant IFN-γ

Imunomax® (IFN-γ1a) is used as a gene recombinant IFN-γ in Japan.

1. Administration method and therapeutic results

In general, gene recombinant IFN-γ is administered by intravenous drip infusion at 2 to 3 MJRU/m^2 every day, or at 10 MJRU/m^2 once daily for 5 days consecutively, which is repeated twice with a withdrawal interval of 9 days. As with IFN-α, the gene recombinant IFN-γ produced variable response rates among medical institutions. A recent report shows a response rate of 10% achieved by once-weekly subcutaneous injection of 2 MJR.[11] A Canadian group reported a response rate of 4.4% in 181 patients with advanced renal cell carcinoma treated with IFN-γ1b once weekly.[12] Horoszewicz *et al.*[4] reported that IFN-γ was effective in 11 of 121 patients (9%) when administered every day or 5 days a week. Previous reports show slightly higher response rates with IFN-α. (Table 1)

2. Adverse reactions

Recombinant IFN-γ causes almost the same adverse reactions as IFN-α, such as fever, leukopenia, thrombocytopenia, depression, and interstitial pneumonia.

Combination of Different Types of IFN or Combination of IFN and Other Drugs

Various combinations including IFN-α have been attempted to improve therapeutic effectiveness.

1. Combination with IFN-γ

IFN-α was combined with IFN-γ to obtain a possible synergistic effect. This was plausible because they bind with different receptors and because IFN-α induces the expression of class I, while IFN-γ induces the expression of Class II. However, the combination failed to provide a higher therapeutic effect than IFN-α alone.[3,13]

2. Combination with retinoic acid

Retinoic acid, which is an active principle of vitamin A, inhibits the proliferation of renal cell carcinoma and increases the antitumor effect of IFN. Motzer *et al.*[14] reported a response rate as high as 30% from this combination. However, recent reports from two medical institutions described a response rate of 4% and 14%,[15] indicating the absence of a combination effect.

3. Combination with IL-2

In a randomized comparative study in which patients were treated with IFN-α alone (18 MU), IL-2 alone (18 MU/m^2), or both, Negrier *et al.*[16] reported the superiority of the combination in response and one-year survival rates. Recently, the combination of low-dose IL-2 and IFN-α with fewer adverse effects has been examined: the regimen involves the subcutaneous administration of 1.8 MU of IL-2 once or twice weekly and intramuscular injection of 1.8 MU of IFN-α for 4 weeks; this comprises one course and is repeated every 3 months. Using the regimen, Buzio *et al.*[17] reported a response rate of 12% and a 3-year survival expectancy of 47% in 50 patients. However, Clark *et al.*[18] who subcutaneously administered the same dose of IL-2 and 8 MU of IFN-α every day reported a response rate of as low as 5.3% and one-year survival rate of 16%. The upper limit of IL-2 covered by the Japanese medical insurance is 2.1 MU. Long-term results from the combination therapy with low-dose IL-2 and IFN are expected.

4. Combination with chemotherapy

The combination with VBL or 5-fluorouracil (5-FU) has been attempted because VBL is the only chemotherapy agent that provided a response rate of about 10% and because 5-FU increased its *in vitro* cytotoxic effect with the addition of IFN-α.

(1) Combination with VBL

This combination has been attempted since around 1985, and has been reported to provide a response rate ranging from 10 to 35%. However, a randomized comparative study comparing IFN alone and combination of IFN and VBL in 3 medical institutions showed no difference in clinical effectiveness, indicating no combination merit[19,20] (Table 2). However, it should be noted that a study reported that a response rate of 15% could be obtained from the combination even in patients who did not respond to IL-2.[21]

(2) Combination with 5-FU

A Japanese multi-center joint study by a research group on renal cancer showed a response rate of 20% (including 3 CR cases) in 53 patients treated with 3 MU of IFN-α and 600 mg/m^2 of 5-FU for 12 weeks[22] (Table 2). However, the result does not surpass results previously obtained with IFN-α alone. Although a combination of IFN-α, 5-FU, and IL-2 has recently attracted attention (Table 3), it produced variable response rates ranging from 2 to 39% among institutions, and the addition of 5-FU tended to increase adverse reactions

Table 2 Combination with IFN-α and Chemotherapy Agents

Reporter (year)	IFN-α	Drug	Number of patients/ efficacy rate (%)	Others
		[VBL] iv		
Sarna, G. (1987)	3MU/5x/w/12wks/im(1) 〃	0.1mg/kg/w (—)	22/14 43/14	No significant difference
Fossa, S.D. (1992)[20]	18MU/3x/w/im 〃	0.1mg/kg/w/every3wks (—)	66/24 79/11	5-year survival rate: 9% 5-year survival rate: 9%
Paolorossi, F. (1995)[21]	3MU/3x/w/sc	0.1mg/kg/w/every3wks	13/15	(Past history with IL-2 therapy)
Tsavaris, N. (2000)[19]	5MU/3x/w/sc 15MU/3x/w/sc	6mg/m^2/w/every2wks (—)	50/18 50/18	No significant difference, response period: 23mos response period: 20mos
		[5Fu] continuous iv		
Elias, L. (1996)	5MU/m^2/1, 3, 5d/w/sc (2)	750mg/m^2/1, 3, 5d/w/ every3wks	40/13	No CR
Igarashi, T. (1999)[22]	3MU/m^2/3x/w/12wks	600mg/m^2/1x/5d→ 1x/w/3~12wks	53/20	
Murphy, B.R. (1992)	9MU/3x/w	750mg/m^2/1~5d/w →1x/w	14/0	Not effective
Haarstad, H. (1994)	12MU/3x/w	600mg/m^2/1x/1~5 d/3 & 4w(3)	31/23	

Response: CR + PR, iv: intravenous, im: intramuscular, sc: subcutaneous, d: day, w: week, wks: weeks, mos: months, →: subsequently
(1): Intramuscular injection of 3M units, 5 days per week for 12 weeks
(2): Subcutaneous injection of 5M units/m^2, 1, 3 and 5 days a week
(3): Three different regimens are available.

Table 3 Combination Therapy of IFN-α, IL-2, and 5-FU

Reporter (year)	IFN-α	IL-2	5Fu	Number of patients/ response rate (%)	Others
Ravaud, A. (1998)	6MU/1x /d/1, 3, 5 d/w sc every 2wks/8wks	9MU/ d /1~6 d/8wks sc	600mg/m^2/1 ~5d/w/1x /4w/ iv bolus	111/2	
van Herpen, C.M. (2000)[24]	6MU/m^2 sc (1) 9MU/m^2/3x /w/5~8wks	20MU/m^2/3x /w/1, 4w sc 5MU/m^2/3x /w/2, 3w	750mg/m^2/1x /w/5~8w Same above	51/12 (total of 2 groups)	No CR Grade 3/4 toxicity: 55.8%
Olencki, D. (2001)[23]	5MU/m^2/1, 3, 5d/w/4wks	5MU/m^2/1~ 5w/4wks sc	300mg/m^2/5x /w/1w	25/28	
Atzpodien, J. (2001)[25]	5MU/m^2/ (2)	10MU/m^2/ (3)	1,000mg/m^2/1 x/d1/5~8w	51/39	CR(7) survival: 24mos

(1) 1x/w/1, 4w & 3x/w/2, 3w: Once weekly in Weeks 1 and 4 and thrice weekly in Weeks 2 and 3
(2) 1x/1d/1&4w, 1x/1, 3d/2 & 3w (increased to 10MUm^2/1, 3, 5 d/5 to 8w
(3) 2x/d/3 to 5d/1 & 4w$^{\#}$ 5x10MUm^2/1, 3, 5d/w/2 & 3w $^{\#}$: twice daily from Days 3 to 5 in Weeks 1 and 4

such as anorexia, fever, malaise, and leukopenia.[23,24] However, since it is expected to improve the response rate and prolong the response period by IL-2, it is necessary to accumulate more clinical results to identify the optimum dose of IL-2 and confirm whether the combination has a long-term tumor reducing effect or not.

Conclusions

Although IFN therapy has provided a response rate of only 10 to 20% in the treatment of advanced renal cell carcinoma, it is expected to prolong survival in patients who respond to it. Combinations with other drugs have been attempted to increase its therapeutic effect. It will be particularly necessary to examine the long-term results of regimens including IL-2.

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Current Clinical Applications of Interferon
—Multiple sclerosis—

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Abstract: Interferon-β-1b (INF-β-1b) has been available in Japan since 2000 as the first therapy to treat relapsing remitting multiple sclerosis (MS). 8 MIU of IFN-β-1b is injected subcutaneously every second day. IFN-β-1b therapy reduces the relapse rate in MS patients. Some biological activities of IFN-β-1b are considered to be inhibitory effects on antigen presentation and proliferation of lymphocytes, and modulation toward anti-inflammation including suppression of interleukin (IL)-12 production from dendritic cells. Adverse reactions associated with IFN-β-1b therapy are as follows: (1) Flu-like symptoms (especially fever, headache, fatigue and myalgia) are experienced by three quarters of patients, but this reaction can usually be managed with NSAIDs and resolved within the first three months after initiation IFN-β-1b treatment. (2) Skin reactions may appear within the first month of treatment. Some of the risk factors in this regard include incorrect injection techniques, use of cold IFN-β-1b solution, and repeated use of the same injection site. (3) A new or exacerbated state of depression may be experienced within the first six months after initiation of IFN-β-1b therapy. (4) Transient increased spasticity usually appears together with flu-like symptoms. (5) One should also note that IFN-β-1b should not be administered to pregnant women, patients with autoimmune hepatitis or with medication containing Sho-saiko-to.

Key words: Multiple sclerosis; Recurrence inhibiting effect; Subcutaneous self-injection; Injection every second day

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system and is characterized by repeated recurrence and remission. As with many other autoimmune diseases, it is likely to occur in people in their twenties to forties, and the ratio of male to female patients is 1 to 1.5–2.0.

MS was until quite recently treated with steroid pulse therapy during its acute stage and with oral steroids and immunosuppressive agents

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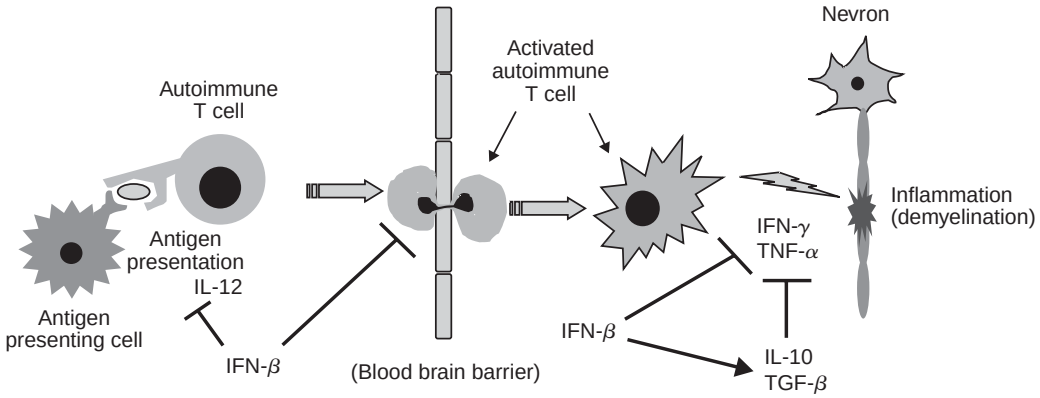

Fig. 1 Action mechanism of IFN-β in inhibiting relapse of multiple sclerosis
IFN-β inhibits interleukin-12 (IL-12) production and antigen presentation of antigen presenting cells, the entry of activated T cells through the blood brain barrier, and the production of IFN-γ and tumor necrosis factor α (TNF-α) from activated T cells. It is known to increase the production of anti-inflammatory cytokines, such as transforming growth factor-β (TGF-β) and IL-10. The (Æ) and (^) symbols indicate the increase and inhibition of each activity, respectively.

for preventing relapse. However, those treatments were often performed based on the experience of the individual physician, with almost no greater body of evidence to indicate their effectiveness. Further to this, interferon-β-1b (IFN-β-1b) was approved in 2000 as the only drug proven to inhibit the recurrence and progress of MS.

This paper describes the current status and clinical practice of the use of IFN-β-1b for MS.

Effects of IFN-β on Multiple Sclerosis (Fig. 1)

The pathophysiology of MS is estimated to advance through the following processes: T cells responding to intracerebral autoantigen are activated to enter the brain and produce IFN-γ and tumor necrosis factor-α (TNF-α), causing inflammation. IFN-β is considered to inhibit autoimmune T cells by inhibiting the production of interleukin-12 (IL-12) (the most important cytokine for inducing IFN-γ) from antigen presenting cells (APCs), or by increasing the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β).[1,2] It is also known to inhibit the proliferation of T cells by reducing the expression of major histocompatibility complex class II (MHC class II) and preventing activated T cells from passing through the blood brain barrier. These effects are also associated with the prevention of the relapse of MS.

Therapeutic Practice for Multiple Sclerosis

Usually, IFN-β-1b is subcutaneously administered at 8 MIU every second day in adult patients with MS. The dose is higher than that used for treating hepatitis or malignant melanoma. Another point that characterizes this therapy is auto-injection. Although the patients inject IFN-β by themselves, it is necessary to hospitalize the patients in introducing the therapy because it is not as easy as, say, using pencil syringes in the treatment of diabetes: it requires each patient to dissolve IFN-β-1b in a solvent and inject 1 m*l* of the solution. Hospitalizing patients is also useful in that any adverse reactions that are likely to develop in the initial stage of the therapy can be immediately treated, and that adequate instructions can be given to the patients and their families to allay their anxieties.

Precautions of IFN Therapy: Adverse Reactions

Most adverse reactions of the IFN-β-1b therapy occur early after it is introduced, and are often controllable. Representative adverse reactions include flu-like symptoms including fever, injection-site reactions, mental changes, and increased spasticity.

(1) Flu-like symptoms

Flu-like symptoms, such as fever, headaches, general malaise, and arthralgia usually develop within 3 to 6 hours after injection and resolve within 24 hours. Fever develops in more than half of patients.[3] These flu-like symptoms often resolve naturally within 6 months; in the meantime, non-steroidal anti-inflammatory drugs (NSAIDs) are used to relieve them. Ibuprofen (400 to 1,200 mg/day) is reported to be more effective than acetaminophen or acetyl salicylic acid.[4] When an NSAID is not enough, oral prednisolone is added (around 10 mg/day).[5] To prevent the discomfort of the flu-like symptoms, patients are recommended to inject IFN-β-1b before going to bed. This will make the adverse reactions resolve by the next morning, and ensure that the injection will be performed after taking a bath. Sleeping keeps patients calm and helps relieve the adverse reactions.

(2) Injection-site responses

More than half of patients treated with IFN-β-1b suffer from injection-site reactions, such as erythema nodosum, and pain. Although these responses are also resolved within 6 months, they occur after every injection, markedly reducing the injectable area. Thus this adverse reaction is most troublesome in continuing IFN-β-1b therapy. To minimize the symptoms, it is necessary to teach patients to master the procedures for preparing and injecting the drug, and to regularly rotate injection sites. It is useful to warm the injection to body temperature. When stronger responses, such as necrosis, are observed, the injection of IFN-β-1b has to be discontinued. Erythema and pain are treated with steroid ointments and icing, respectively.

(3) Mental change

As with other types of IFN, IFN-β-1b causes symptoms of depression, such as anxiety and despair. The treatment for these symptoms is not described here, and the reader is asked to refer to the appropriate articles.

(4) Increased spasticity

Existing symptoms of MS may transiently worsen. Attention should be paid to the fact that the worsened symptoms are easily mistaken for relapse. The worsening of existing symptoms mostly occurs as increased spasticity, although reduced visual acuity and sensory disturbance have also been reported. These symptoms often occur within 3 months after IFN-β-1b therapy is started. Since most of them are transient and resolve satisfactorily, it is necessary to give a full explanation to the patients to prevent them from discontinuing IFN-β-1b. Since increased spasticity often occurs with the above flu-like symptoms, it is treated with NSAIDs or muscle relaxants, such as baclofen. In the patients who have been treated with a muscle relaxant, increasing the dose of relaxant often relieves increased spasticity.

(5) Others

Other adverse reactions include leukopenia, hepatic dysfunction, abnormal laboratory values, and worsened diabetic control. It should be noted that abnormal glucose tolerance is often overlooked in the blood test for non-diabetic patients. Combination with Sho-saiko-to is contraindicated because it may cause interstitial pneumonia. Attention should be paid to the treatment of patients with autoimmune diseases other than MS. In particular, IFN-β is contraindicated in patients with autoimmune hepatitis. IFN-β is also contraindicated in pregnant or lactating women. Since multiple sclerosis often develops in women with pregnancy potential, it is necessary to inquire about the future childbearing plans of patients before introducing IFN therapy.

Opinions from Patients

A questionnaire survey by the MS CABIN (Japanese Branch of the International Multiple Sclerosis Support Foundation; http://www.mscabin.org/) showed that the patients had the following negative feelings before the introduction of IFN therapy: (1) vague fear of injection (40%); (2) anxiety about continuing the therapy (14%); (3) anxiety about injection technique (7%); and (4) a sense that the explanation from the attending physician was inadequate (5%). It is important to obtain trust from the patients before introducing IFN therapy, and most of these negative feelings can be overcome by giving patients full explanation and guidance. Since the survey also showed that 17% of patients could overcome the negative points through cooperation with their families, it is also necessary to give a full explanation and guidance to their families. It is also necessary to explain that IFN reduces recurrence, severity, and lesion area as determined by MRI, but does not completely inhibit the disease: the patients who expect too much of IFN tend to fail to comply properly with the therapeutic procedures.

Future Development of IFN

IFN-β-1a (Avonex), a type of IFN with the same amino acid sequence as natural-type IFN-β, is now being examined in a clinical study. It is characterized by the finding that neutralizing antibodies for it are unlikely to develop. The drug is intramuscularly injected once weekly, and is expected to be effective for patients with severe injection-site responses to IFN-β-1b preparations.

Conclusions

IFN-β-1b has become available as a drug with proven effectiveness in inhibiting the relapse and progression of MS. Since it can be relatively safely self-injected by patients (so long as full explanations and guidance are provided), clinicians should actively put it into clinical practice as a standard therapy, much as they would recommend insulin therapy for diabetes.

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Practice of Interferon Therapy
—Chronic hepatitis C (combination with ribavirin)—

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Abstract: Interferon (IFN) plus ribavirin therapy over 24 weeks resulted in a 20% complete response (CR) in chronic hepatitis C (CH-C) patients who had relapsed on IFN monotherapy in Japan. As we reported previously, the serum amount of HCV RNA decreases biphasically during IFN therapy in CH-C patients. It has been considered that the first phase reflects a direct antiviral effect of IFN and the second phase might reflect antiviral activity and elimination of hepatocytes by apoptosis which might be induced by activated CTL. The second phase might be an important factor in achieving a complete response (CR) in antiviral therapy. Serum HCV RNA level, HCV genotype, amino acid changes in NS5A region, and stage of liver fibrosis are important predictive factors in IFN monotherapy in CH-C patients. However, these factors were not so useful for predicting CR in IFN/ribavirin therapy in the Japanese study. To clarify the predictive factors on IFN/ribavirin in CH-C patients, we are going to study HCV dynamics, changes of Th1/Th2 balance in peripheral blood, and changes of receptors of Th1 and Th2 in peripheral blood on IFN/ribavirin therapy in CH-C patients.

Key words: Chronic hepatitis C; Interferon; Ribavirin; HCV dynamics; First phase; Second phase

Introduction

In Japan, there have been hundreds of thousands of patients with intractable chronic hepatitis C who have not responded to interferon (IFN) therapy in Japan. The combination of IFN/ribavirin, which became covered by the Japanese medical insurance in December 2001, can treat around 20% of such patients. Although only the data from clinical studies are available for the follow-up results for many patients, this paper describes the indications, therapeutic outcomes, and adverse reactions of the combination therapy. The combination

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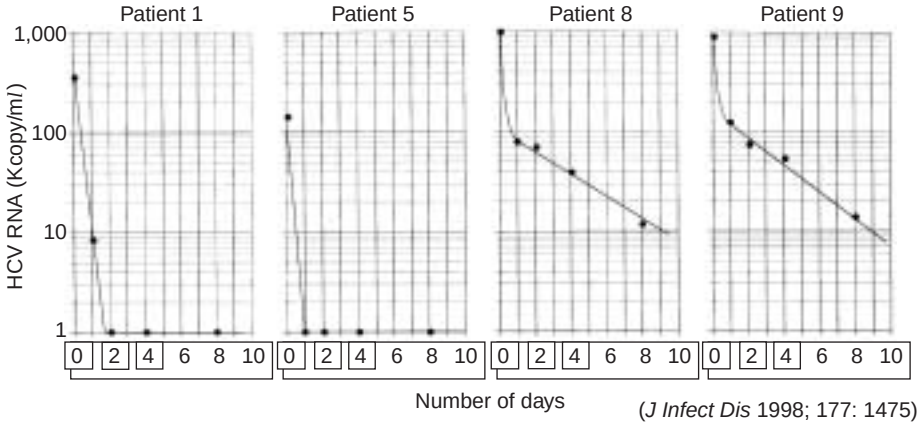

Fig. 1 Blood HCV RNA dynamics during IFN therapy

therapy has been used widely over the past few years in Western countries. The combination of peginterferon (Peg-IFN), a long-acting preparation of IFN, and ribavirin, is now the standard therapy for intractable hepatitis C.

Characteristics of IFN/Ribavirin Combination Therapy

IFN has both antiviral and immunomodulating effects. Ribavirin (Rib) is a nucleic acid derivative with a relatively weak antiviral effect. It mainly acts on the immune system: it inhibits the Th2 system to make the Th1 system relatively superior, and it directly stimulates the Th1 system.[1–3] The IFN/Rib combination therapy produces a significantly higher response rate than the IFN therapy alone in patients with chronic hepatitis C.

We previously examined the blood HCV dynamics after the consecutive administration of IFN in patients with chronic hepatitis C, and reported that the serum amount of virus (amount of HCV RNA) was reduced in a biphasic manner[4]: the serum amount of virus was acutely reduced in the first 24 hours (1st phase, half life: 5 to 7 hours) and then slowly in the subsequent period (2nd phase, half life: 70 to 100 hours) (Fig. 1).[4]

The HCV dynamics after the administration of IFN can be roughly divided into 4 patterns: (1) the HCV RNA amount is sharply reduced to 10 to 1% (or lower) of that of the pretreatment level, and comes close to or falls below the minimum limit of determination in the 1st phase; (2) the HCV RNA amount is reduced to around 10% of that of the pretreatment level in the 1st phase, with a subsequent half life that is 5 to 10 times as long as that of the 1st phase; (3) the HCV RNA amount is significantly reduced in the 1st phase, followed by poor reduction during the second phase, with HCV RNA remaining positive even after several months; and (4) no significant viral reduction during either the 1st or 2nd phase.

It is considered that the 1st phase represents the direct antiviral effect of IFN, while the 2nd phase represents the antiviral effect plus the removal of infected hepatocytes by cytotoxic T lymphocytes (CTL).[5] Hepatitis C with the above (3) or (4) HCV dynamics pattern cannot be eliminated with IFN therapy. It is assumed that the IFN/Rib combination may increase the antiviral effect of IFN and stimulate CTL to remove infected hepatocytes and reduce the half-life of the 2nd phase, resulting in an increase in the rate of marked response. In fact, clinical results supporting this assumption have been reported.[6,7] It is possible that some of the patients who showed the above (2) or (3) pattern after IFN therapy may well respond to the IFN/Rib combination.

Indications

Basically, the indications of the IFN/Rib combination are the same as those of IFN therapy. However, it should be noted that Rib dose-dependently causes hemolytic anemia, and that it is contraindicated in patients with a pretreatment hemoglobin level of 12 g/dL or lower because it reduces hemoglobin by 3 to 4 g/dL, on an average. Other adverse reactions to the combination therapy are similar to those of IFN therapy. However, general malaise, anorexia, alopecia, and eruptions tend to be slightly severer with the combination therapy. Therefore, it is generally contraindicated in patients of 70 years or older, and should be carefully administered in patients of 65 years or older.

Table 1 Therapeutic Efficacy of IFN in 1,370 Patients with Chronic Hepatitis C

Disease stage	Therapeutic efficacy of IFN (biochemical efficacy determination)		
	Marked response	Transient response	No response
F1 ($n=229$)	101 (44%)	76 (33%)	52 (23%)
F2 ($n=710$)	236 (33%)	195 (27%)	279 (40%)
F3 ($n=383$)	85 (22%)	80 (21%)	218 (57%)
F4 ($n=48$)	4 (8%)	7 (15%)	37 (77%)
Total 1,370	426 (31%)	358 (26%)	586 (43%)

(Okanoue, T. *et al.*: *Hepatol Res* 2002)

Therapeutic Practice and results

Important predictive factors for the therapeutic efficacy of IFN for chronic hepatitis C include serum viral amount, HCV genotype, and severity of hepatic fibrosis. Table 1 shows the efficacy of IFN in 1,370 patients with hepatitis C by the disease stages (severity of fibrosis). It shows that 31% of the patients markedly responded to IFN.[8] It should be noted that since 10% of the 31% still had viremia, they are so-called biochemically marked responders.

The Japanese clinical study for developing the IFN/Rib combination therapy was performed in intractable cases with a genotype of 1b and HCV RNA amount of 1 Meq/mL or higher. The following 3 groups were set in the study: a group treated with IFN at 6 MU/day (6 MU/day for 2 weeks consecutively followed by thrice weekly) and Rib; a group treated with IFN at 10 MU/day (10 MU/day for 2 weeks consecutively followed by thrice weekly at 6 MU/day) and Rib, and a group treated with IFN alone. All three groups were treated for a total of 24 weeks. The rate of marked responders was 2.3% in the IFN group and around 20% in the IFN 6 MU/day + Rib combination group (Table 2). Rib was administered at a dose of 600 mg/day in patients weighing 60 kg or less and 800 mg/day in those weighing 61 kg or more. The patients who entered the study were intractable cases, and about three quarters had been treated with IFN without sufficient re-

Table 2 IFN/Rib Combination Therapy for Intractable Chronic Hepatitis C (comparison with IFN therapy)

Therapeutic contents	Marked response rate
rIFNα-2b, 6 MU for 2 weeks continuously, followed by 6 MU thrice weekly for 22 weeks plus ribavirin	20.2% (18/89)
rIFNα-2b, 10 MU for 2 weeks continuously, followed by 6 MU thrice weekly for 22 weeks plus ribavirin	17.0% (16/92)
rIFNα-2b, 10 MU for 2 weeks continuously, followed by 6 MU thrice weekly for 22 weeks (IFN alone)	2.3% (2/88)

Patients with a gene type of 1b and large amounts of virus in the blood were treated, and about 75% of them had shown no response to IFN alone.

sults. About 50% of them were very intractable with an HCV RNA amount of 850 KIU/mL or higher. The results obtained were not so different from those obtained in Western countries. In Western countries, IFN/Rib combination therapy is given for 48 weeks in intractable chronic hepatitis C patients,[9] and the combination of Rib and Peg-IFN, a long-acting preparation of IFN, has recently become the first line therapy for intractable chronic hepatitis C.[10,11]

Since the rate of marked response in the IFN/Rib combination therapy is proportional to the blood Rib concentration, Rib should be administered at 1,000 mg/day in patients weighing 75 kg or more.

Predictive Factors of Efficacy

Serum viral amount, genotype, and severity of hepatic fibrosis are important factors that influence the therapeutic efficacy of IFN therapy. The rate of marked response by IFN is almost 0% in patients with a serum viral amount of 850 KIU/mL or more. In contrast, the IFN/Rib combination therapy in patients with a genotype of 1b and a large serum viral amount showed a marked response rate of 19.2% in the group treated with 6 MU/day of INF even in patients with a serum viral amount of 850 KIU/mL or more. This indicates a certain rate of marked response can be expected from the combination therapy in patients with a high viral amount. Although the marked response rate of IFN therapy is significantly reduced as hepatic fibrosis progresses, it is not so reduced as the IFN therapy in patients treated with the combination therapy (F1: 23%, F2: 18%, and F3: 15%). Therefore, it is impossible to accurately predict the efficacy of the IFN/Rib combination therapy, and it is worth trying it in any patients for whom it is indicated.

The presence/absence of blood HCV RNA at 4 or 12 weeks after the start of treatment is an important predictor for the efficacy of the ongoing combination therapy: 56% of those negative for blood HCV RNA determination at 4 weeks recovered completely, and 27% of those positive at 4 weeks but negative at 12 weeks showed marked response. In contrast, there is little possibility of recovery for those positive for HCV RNA at 12 weeks.

We are now examining the relationship between HCV dynamics and Th1/Th2 balance or the expression of Th1 and Th2 cytokine receptors to identify a predictive factor of the efficacy of the IFN/Rib therapy. It is considered important to stimulate the Th1 system by Rib and increase the antiviral effect of IFN by the combination in order to treat patients not responding to IFN therapy with the IFN/Rib combination therapy.

Adverse Reactions

As described above, Rib surely causes hemolytic anemia. Rib should be reduced when Hb falls to 10 g/dL, and returned to the original level when Hb increases. Anemia is most likely to occur 2 to 4 weeks after the start of treatment, although it may progress after 4 weeks.

The IFN/Rib combination therapy should be given carefully to patients with hypertension or diabetes, particularly those with a change of the fundus occuli, because they may develop cerebral hemorrhage during treatment.

Conclusions

IFN-Rib combination therapy is the first line therapy for intractable chronic hepatitis C. However, because much remains to be improved (such as lessening the relatively severe adverse reactions), it should be applied carefully.

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Practice of Interferon Therapy
—Chronic hepatitis C (Therapy with consensus interferon)—

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Abstract: The consensus interferon, rIFN-αcon1, has been proved to be effective for the treatment of chronic hepatitis C (CH-C) with genotype 1b and high viral load (≧100 kc/m*l*) through randomized controlled studies performed in Japan. For patients with genotype 1b and high viral load, the complete response rate (16.7%) of rIFN-αcon1 (18MU) is significantly higher than that of IFN-nα (6MU), though it is 0% in those with a viral load of more than 700 kc/m*l*. rIFN-αcon1 is also effective for the treatment of CH-C patients with both low viral load and a history of prior IFN treatment. It will be concluded that rIFN-αcon1 is effective for CH-C patients with a viral load of less than 700 kc/m*l*.

Key words: Chronic hepatitis C; High viral load group; Consensus interferon

Introduction

The therapeutic strategy for chronic hepatitis C has changed dramatically since consensus interferon (rIFN-αcon1, Advaferon) and the ribavirin (Rebetol) + IFNα-2b (Intron A) combination therapy were approved in December 2001 and the limitations to the administration period of existing IFN-α preparations were abolished in February 2002.

This paper describes the indications and future issues for rIFN-αcon1 based on clinical study results.

Outline of rIFN-αcon1 (consensus interferon)

This preparation has 166 amino acid residues and a molecular weight of 19,500 Daltons. The number of amino acid residues is almost the same as that of existing IFN-α preparations. Thirteen subtypes of IFN-α with different activities were known in 1982. A new amino acid sequence was designed according to the hypothesis that a useful IFN preparation could be created by choosing a frequent amino acid at each site of amino acid sequences (consensus-sequence theory; Fig. 1).[1] rIFN-αcon1 was produced with synthetic DNA based on the amino

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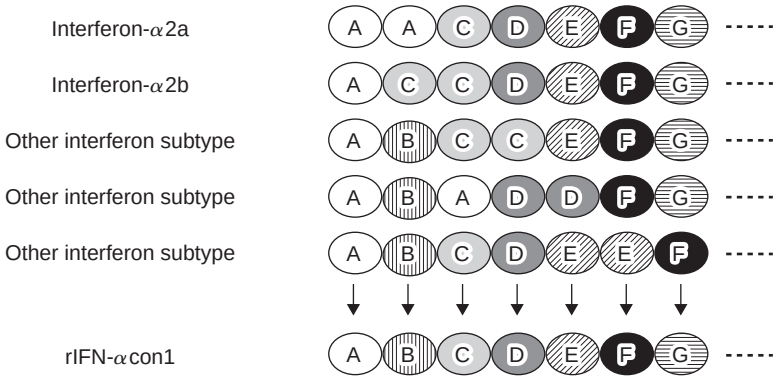

Fig. 1 Design of amino acid sequence for rIFN-αcon1

acid sequence in a gene-recombinant *Escherichia coli* expression strain. Since this preparation had a high affinity for Type 1 IFN receptors[2–4] and was superior to a control IFN preparation in antiviral effect,[5–7] cell growth-inhibiting effect,[8] and immuno-stimulating effect,[5,8] clinical studies were started in 1991 in USA and in 1993 in Japan.

Unlike existing IFN-α preparations, it is supplied as a subcutaneous injection at a small volume (0.4 m*l* for 12 MIU and 0.6 m*l* for 18 MIU) without human serum-derived albumin.

Clinical Results of rIFN-αcon1

Although rIFN-αcon1 has been clinically applied, no major results have been published yet. Therefore, the results of a randomized controlled study using the IFN-αn1 preparation as a control are described here.[9,10] rIFN-αcon1 was subcutaneously administered at 18 or 12 MIU/day for 2 weeks consecutively, followed by thrice weekly for 22 weeks to determine the rate of patients with virologic complete response (CR) (defined as negative for amplicor determination) and normal ALT at the time after 24 weeks from the end of treatment.

1. Group with high viral load (≥100 kcopies/m*l* or ≥1 Meq/m*l*)

rIFN-αcon1 produced a CR rate of 26.3%

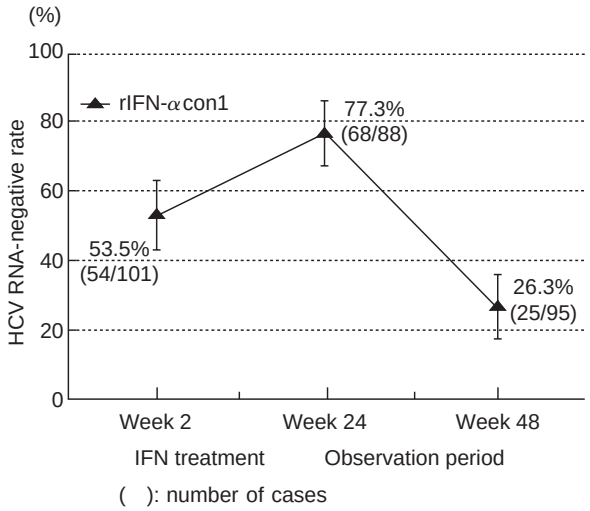

Fig. 2 Change in HCV RNA-negative rate in patients with high viral load

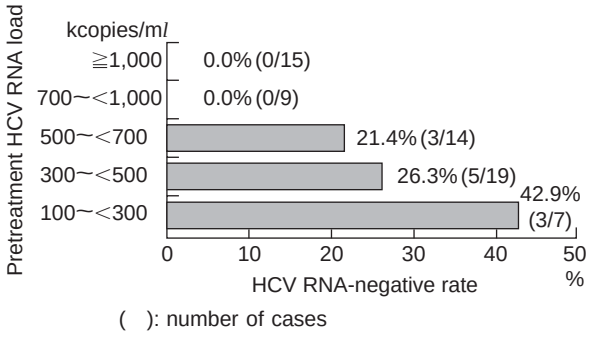

Fig. 3 HCV RNA-negative rate by viral loads in patients with genotype 1b and high viral load

Table 1 HCV RNA-Negative Rate by Genotypes in Patients with Low Viral Load

	Genotype			Total
	1b	2a	2b	
HCV RNA-negative rate (%) (No. of cases)	71.4 (10/14)	75.0 (12/16)	—	73.3 (22/30)

Table 2 HCV RNA-Negative Rate by Viral Loads and Genotypes in Patients Treated with IFN for the Second Time

Pretreatment viral load (kcopies/m*l*)	Genotype			Total
	1b 12.5% (2/16)	2a 100% (9/9)	2b 30.0% (3/10)	40.0% (14/35)
≥100	6.7% (1/15)	100% (3/3)	37.5% (3/8)	26.9% (7/26)
<100	100% (1/1)	100% (6/6)	0.0% (0/2)	77.8% (7/9)

( ): number of cases

(25/95) (Fig. 2) and a normal ALT rate of 43.8% (35/80) in the 18 MIU treated group. It produced a CR rate of 16.7% (11/60) and normal ALT rate of 35.1% (20/57) in the patients with hepatitis of genotype 1b, who are considered particularly intractable among those with high blood viral load. The CR rate was significantly higher than that of the control group ($p<0.05$). The CR rate was also higher than that of existing IFN-α preparations (0 to 8.6%). Figure 3 shows the CR rate by pretreatment viral load in patients with hepatitis of genotype 1b and high viral load. Although the CR rate tended to fall as the viral load was increased, a high CR rate of 27.5% (11/40) was obtained for the group with a viral load from 100 to less than 700 kcopies/m*l*. In contrast, rIFN-αcon1 produced a CR rate of 0% in patients with a very high viral load of 700 kcopies/m*l* or higher.

2. Group with low viral load (<100 kcopies/m*l* or <1 Meq/m*l*)

rIFN-αcon1 at 12 MIU produced a CR rate of 73.3% (22/30), with no difference among genotypes (Table 1). It was more effective than existing IFN-α preparations (49.1 to 66.0%) in the patients with low viral load as well.

3. IFN re-treatment group

rIFN-αcon1 was administered at 18 MIU in patients in whom previous IFN therapy made HCV RNA negative or ALT return to normal, but did not achieve CR. The results showed it achieved CR in 40.0% (14/35) and made ALT persistently normal in 51.5% (17/33) (Table 2). This indicates that the preparation is clinically significant for those re-treated with IFN as much as for those treated for the first time. In addition, rIFN-αcon1 produced a CR rate of 0% in patients with hepatitis of 1b genotype and a high viral load of 300 kcopies/m*l* or higher.

4. Safety

All the 227 patients treated with rIFN-αcon1 experienced at least one adverse reaction: fever developed in 98.2%, general malaise in 45.4%, anorexia in 39.6%, headaches in 39.2%, arthralgia in 32.6%, insomnia in 27.8%, alopecia in 27.8%, and gastric discomfort in 20.3%. Although all these adverse reactions

were already known, it should be noted that they tended to develop at higher incidences than with previous IFN-α preparations. Depression, a serious adverse reaction to IFN, was observed in 5% or higher. Sho-saiko-to is contraindicated in patients treated with rIFN-αcon1. Further, it is recommended that the combination of rIFN-αcon1 with theophylline, antipyrine, or warfarin be performed with care because the IFN preparation inhibits the activities of enzymes responsible for drug metabolism in the liver.

Indications and Future Issues of rIFN-αcon1

Considering the above clinical results, this preparation is indicated for patients with 1b genotype and a high viral load of up to 700 KIU/m*l*, in addition, it is expected to show higher efficacy than existing IFN-α preparations in the groups with 2a genotype and high viral load, or with low viral load. Although the ribavirin + IFN-α2b combination therapy is also indicated for patients with a high viral load, it has a drawback in that ribavirin causes hemolytic anemia. Therefore, rIFN-αcon1 is recommended as the first line treatment for the patients with blood Hb around 12 g/d*l* or lower. Since the clinical study of this preparation was performed in a relatively small number (less than 300) of patients, it goes without saying that verifying the efficacy and safety of rIFN-αcon1 is required.

To further improve the therapeutic results of rIFN-αcon1 in patients in the intractable 1b/high viral load group, it would be valuable to create a polyethylene glycol (PEG) preparation of rIFN-αcon1 or combine rIFN-αcon1 with ribavirin.

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Neuropsychiatric Symptoms Related to Interferon Therapy

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Abstract: The severity and duration of side effects of interferon (IFN) therapy vary considerably. The neuropsychiatric symptoms induced IFN therapy are the most frequent reason for discontinuing it. The incidence of neuropsychiatric symptoms is as high as 30 to 40% when mild neuropsychiatric alterations are included. Among various neuropsychiatric symptoms, affective disorders such as depression are predominant, followed by cognitive disorders such as delirium. Others include insomnia, anxiety, irritability, mania, delusion, hallucination, and change to aggressive personality. Neuropsychiatric symptoms occur at a wide range of times during IFN therapy. Characteristics of patients at risk of experiencing neuropsychiatric symptoms during IFN therapy include high age, high dosage of IFN, severe comorbid physical disorders, a history of psychiatric illness, neurotic premorbid personality, organic brain disease, family history of psychiatric illness, severe depression/somatic anxiety/sleep disturbance before treatment, and low degree of informed consent to IFN therapy. In general, dosage reduction or discontinuation of IFN is recommended in cases of IFN neurotoxicity. If necessary, psychotropic agents are to be administered. We should make carefully and early intervention in any case where there is evidence of possible suicidal tendencies.

Key words: Interferon; Depression; Suicide; Delirium; Side effect; Neurotoxicity

Introduction

Among various side effects of interferon (IFN), neuropsychiatric side effects are frequently observed and most likely to prohibit the continuation of the therapy. Suicide attempts related to IFN therapy are a particularly serious concern. Therefore, IFN should be used under careful monitoring.

Diagnosis of Drug-Induced Mental Disorders[1,2)]

It is important to clarify the time relationship

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Table 1 Characteristics of Neuropsychiatric Symptoms Related to Interferon

1. Most of the neuropsychiatric symptoms of IFN are depression, and the remainder are forms of delirium.
2. Depression often develops as psychomotor retardation or anxiety/irritability with aggressiveness
3. Insomnia often precedes depression. Sometimes severe depression occurs suddenly and the patient becomes suicidal.
4. Approximately 10% of patients with chronic hepatitis C develop neuropsychiatric complications requiring treatment with psychiatric drugs or discontinuation of IFN therapy. About 30–40% of patients experience mild psychiatric complications
5. Neuropsychiatric symptoms occurred at a wide range of times during IFN therapy.
6. Most neuropsychiatric symptoms disappear within several days to 2 weeks after discontinuation of IFN therapy, but some may persist.
7. In some patients who have no clouding of consciousness, EEG abnormalities such as slowing of background activities is also observed.

(Kamijima, K. and Otsubo, T.: Progress in hepatology, volume 2. *Interfeon Therapy on Chronic Hepatitis C.* 1996; pp. 67–86, Elsevier Science, Amsterdam. Otsubo, T.: *Jpn J Psychiatr Treat* 1996; 11: 121–131.)

between the onset of drug-induced neuropyschiatric symptoms and drug administration. A neuropsychiatric symptom is suspected to have a causal relationship with IFN when it occurs immediately after the start of IFN therapy, or when it improves or disappears after the reduction or discontinuation of the therapy. However, neuropsychiatric symptoms may occur at a wide range of times during IFN therapy. Some neuropsychiatric symptoms may occur several months after the start of IFN therapy, or may be more persistent after IFN is discontinued. A relationship with IFN can be suspected when there is discontinuity from the premorbid personality, or an acute change in neuropsychiatric symptoms is observed.

Psychological Factors of Patients with Indications of IFN Therapy

It has been pointed out that important psychological factors affect chronic hepatitis C patients treated with IFN. The patients know that in most cases chronic hepatitis C progresses to liver cirrhosis and hepatic cell carcinoma if it is not treated promptly, and IFN is effective in only about 30% of chronic hepatitis patients. IFN is being used for the treatment of different malignancies, such as multiple myeloma, and chronic myelogenous leukemia. It is therefore important to note that the psychological factors of patients with the indications for IFN are far from normal.

Neuropsychiatric Symptoms Related to IFN Therapy[1–6] (Table 1)

1. Incidence of neuropsychiatric symptoms

To summarize the previous reports,[1–6] approximately 10% of patients with chronic hepatitis C develop neuropsychiatric complications requiring treatment with psychiatric drugs or discontinuation of IFN therapy. About 30–40% of patients with hepatitis C experience mild psychiatric complications such as insomnia, loss of interest, agitation, and anxiety.

2. Classification of neuropsychiatric symptoms

Although neuropsychiatric symptoms of IFN vary, affective disorders such as depression are most frequent, followed by cognitive disorders including delirium. Others include insomnia, anxiety, irritability, mania, delusion, hallucination, and change to aggressive personality.

3. Onset and duration

Influenza-like symptoms such as fever, headache, fatigue, anorexia, nausea, vomiting, and insomnia develop within one week after the start of IFN therapy. Since these primary symptoms cause both physical and neuropsychiatric discomfort, the failure to appropriately treat them leads to persistent insomnia and anxiety, which form a basis for secondary neuropsychiatric symptoms.

During the intermediate stage of IFN therapy (from weeks 1 to 8), the following symptoms may occur: insomnia, anxiety, irritability, depression, mania, delusion, hallucination, and change to aggressive personality, delirium, and

Table 2 Possible Risk Factors for Neuropsychiatric Symptoms of IFN

1. High dosage (One day dosage)
2. High age
3. Organic brain injury or dysfunction (atrophy, trauma, metastatics, etc.)
4. Current or previous psychiatric diagnosis
5. Drug and alcohol abuse
6. Depressive state before the start of IFN therapy
7. Sleep disturbance before the start of IFN therapy
8. Strong anxiety for somatic disorders (HCV, RCC, CML, etc.)
9. HIV infection
10. Premorbid personality (neurotic, typus melancholicus)
11. Personality disorder

(Otsubo, T.: *J Showa Med Assoc* 2003; 63: 14–20. Schaefer, M. *et al.*: *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26: 731–746.)

confusional state.

During the last stage of treatment (2 months and later), patients often experience insomnia, continued fatigue, and depression.

High-dose IFN therapy may cause IFN cerebropathy in patients with malignant tumors. It is characterized by somnolence, delirium, confusion, mental and motor slowing, difficulty in concentrating, memory impairment, and seizures, and it is associated with electroencephalogram (EEG) abnormality such as slowing of background activities.[7)]

4. Risk factors[1,2,6)] (Table 2)

The risk factors of neuropsychiatric symptoms are classified into drug and patient factors. Drug factors include dosage (high dosage), application form (intracerebroventricular> intravenous> intramuscular> subcutaneous), and schedule of IFN therapy (everyday> intermittingly), while patient factors include the type and severity of underlying disease (malignancy> hepatitis), comorbid chronic physical disorders, premorbid personality (neurotic or typus melancholicus), history of psychiatric illness and organic brain disease (brain injury, atrophy, trauma, metastasis), family history of psychiatric illness, (low) degree of informed consent to IFN therapy, and age (high age).

Depression, Suicidal Ideation, and Suicide Attempts as the Most Serious and Life-Threatening Adverse Reactions Requiring Full Attention

The investigation by the Ministry of Health and Welfare[8)] into 32 patients who attempted suicide (including 12 who died by suicide) showed that about 80% of them attempted suicide within three months from the start of IFN therapy, and that 20% had a history of depression or psychiatric disorders. Typical cases impulsively and suddenly attempted suicide in a negligent, impatient, and desperate mood after they expected insomnia, anxiety, and irritability for more than two weeks persistently. It should be noted that they attempted suicide with no clear forewarning.

Our prospective study led by Otsubo[5)] showed that 37.3% of 85 patients with hepatitis C had depression during IFN therapy, and that the following factors could indicate a depressive state: neurotic premorbid personality, severe depression, insomnia and anxiety about disease before IFN therapy. Typical symptoms associated with depressive states include being easily tired, loss of ambition, and loss of thought or concentration. Most patients experience insomnia before entering a depressive state, but sometimes severe depression occurs suddenly in one or two days and the patients become suicidal.

Putative Mechanisms Underlying IFN-Induced Neuropsychiatric Symptoms[1–6)]

(1) IFN is indicated for serious disease with relatively poor prognosis, such as chronic active hepatitis C, renal cell carcinoma, multiple myeloma, and chronic myelogenous leukemia. Since the patients have obtained substantial medical knowledge from the mass media, many patients tend to be pessimistic. Such diseases restrict the social activities of the patients, and the patients encounter economic difficulties and a poorer

quality of life. Under these situations, the patients readily feel hypochondriac, desperate, and depressed and have only pessimistic views of their future. It is inevitable that this may lead to suicidal ideation and thence to suicide attempts.

(2) The direct cytokine effect of IFN on the central nervous system (CNS) or the neurotoxicity of cytokines induced by IFN may also influence the CNS.[9] IFN stimulates the activation of neurons, induces convulsions, and increases slow waves in EEG.[10] However, these phenomena have not been fully explained because IFN is hardly able to cross the blood-brain barrier (BBB) and has a short half-life. Nevertheless, IFN enter the brain via the circumventricular organs associated with the hypothalamus, where is no BBB. This enables it to directly influence the brain.

(3) IFN is known to induce production of secondary cytokines, such as IL-1 and tumor necrosis factor (TNF), which may be neurotoxic. IL-1 induces fever, sleep associated with slow EEG activity, and loss of appetite, and stimulates the hypothalamic-pituitary-adrenal (HPA)-axis. IFN is structurally and functionally similar to neuroendocrine hormones, such as ACTH, and the plasma cortisol level has been reported to increase during IFN therapy. It has been suggested that the HPA-axis stimulation caused by IFN is related to the occurrence of depression or suicide.[11]

(4) IFN has also been shown to have opiate-like neurotransmitter activity, and IFN may reduce the activities of noradrenaline in the locus ceruleus mediated by opiate receptors.[12]

(5) It is also possible that the malignant tumors or hepatitis virus for which IFN is indicated may be directly involved in neuropsychiatric symptoms.

Treatment of Neuropsychiatric Symptoms Associated with IFN[1–6]

(1) If neuropsychiatric symptoms occur with IFN therapy, dosage reduction is often recommended, and if serious suicidal ideation occurs, IFN is usually discontinued and the patient hospitalized.

(2) Appropriate psychotropic drugs should be administered if psychiatric symptoms persist after IFN is discontinued. Anxiolytic drugs should be administered for anxiety, irritability, and insomnia. Unlike other benzodiazepine anxiolytic drugs, lorazepam (Wypax) is directly glucuronate- conjugated and quickly excreted, and this metabolic pathway is maintained even in patients with advanced hepatic disease. Lormetazepam (Evamyl/Loramet) is recommended as a hypnotic for insomnia because of its one-step metabolic pathway.

Previously, depression, suicidal ideation, and suicide attempts were treated with tricyclic antidepressants such as amitriptyline (Tryptanol), which have both antidepressant and sedative effects, although they may cause dry mouth, dysuria, constipation, or eye modulation disorder. Some selective serotonin reuptake inhibitors (SSRIs) with almost no such anticholinergic effects have recently became available in Japan: they include fluvoxamine (Depromel/Luvox) and paroxetine (Paxil). Although they are useful and have fewer adverse reactions, they often cause digestive disorder. Milnacipran (Toledomin), a serotonin and noradrenaline reuptake inhibitor (SNRI), is safe due to its lack of interaction with other drugs.

For psychotic symptoms including hallucination/delusion and excitement, antipsychotics, such as haloperidol (Serenace), are often selected, although they caused extrapyramidal symptoms (EPS) at high incidences. Recently, antipsychiatrics with fewer EPSs and little effect on the cardiac circulation system have been increasingly used: such drugs include risperidone (Rispadal), olanzapine (Zyprexa), quetiapine (Seroquel), and perospirone (Lullan).

(3) There are various IFN preparations, and it has not been determined which preparation is likely to cause psychiatric symptoms. It is worth trying to switch from one IFN preparation to another.

Incidentally, the treatment of chronic hepa-

titis C, which had almost reached its limit with conventional IFN therapies, has entered a new paradigm with new therapeutic techniques from Western countries. They include therapy with consensus interferon (cIFN) obtained by the molecular-biological synthesis of parts common to many of 13 subtypes of IFN-α and the use of Peg-IFN, which extends the drug's activities for a long period due to the combination with polyethylene glycol. Further, the combination therapy of IFN and ribavirin has become a standard therapy for chronic hepatitis C in Western countries because it has a markedly increased complete response rate. Ribavirin is a quanosine derivative that acts widely on DNA and RNA viruses. Maddrey,[13] who investigated the adverse reactions of combination therapy in 2,089 patients, noted that suicide was attempted by 24 patients, including 14 who had a history of suicide attempts. However, he considered that the psychiatric symptoms were mainly attributable to IFN and not worsened by ribavirin.

Prevention of Neuropsychiatric Symptoms Induced by IFN[14]

(1) It is necessary to carefully examine whether the target disease responds to IFN or not and strictly decide whether IFN is indicated for it or not. For chronic hepatitis C, viral type and amount, progression, and the balance of benefit and risk should be considered in deciding the type, dosage, and administration method and period of an IFN preparation to be used.

(2) In principle, IFN should not be used for patients with a history of psychiatric disorder. IFN should be administered under strict control in patients who have a family history of psychiatric disorder. IFN should be immediately discontinued if any psychiatric symptom occurs.

It is necessary to inquire into the history of depression or depressive state in detail: the main symptoms, clinical course, and treatment given in medical institutions are important items of information. Since depression is associated with high familial aggregation, it is necessary to inquire as to whether there is any family history of psychiatric disorders. The following questions are typically asked: "Have you ever felt depressed or miserable without specific reason?", "Have you ever felt any loss of energy or difficulties in continuing your work?", "Have you ever experienced loss of interest in your favorite TV programs or books?", and "Have any of your family members committed suicide?" If a patient clearly has a history of depression, it is necessary to discuss with the patient whether IFN should be ruled out, or started only under strict monitoring. It is also important to inform the patient's family members that psychiatric symptoms may occur, and that they have to carefully observe the patient and keep communicating with the medical professionals concerned.

(3) Patients and their families must be informed of what chronic hepatitis C is, what IFN therapy is, and possible side effects of IFN therapy. Furthermore, physicians should remember to inform them that IFN therapy is not the only choice for treatment of chronic hepatitis C, if the therapy is discontinued because of side effects. Psychotherapy, such as supportive psychotherapy, may be effective for treating IFN-induced depression.

(4) Pyschiatrists can advice physicians specializing in other fields of medicine on how to diagnose, treat, and handle the psychiatric state and behavior of patients. This function is called consultation. Psychiatrists can organize medical teams based on continuous cooperative relationships with physicians specializing in other fields of medicine, nurses, and caseworkers to help handle, and give instructions on, psychiatric issues in other departments. This function is called liaison. Putting consultation-liaison psychiatry into practice will help prevent adverse reactions to IFN.

(5) It is necessary for medical professionals who handle any IFN preparation to carefully read its attached papers and fully understand it.

All IFN preparations have a warning about suicide attempts, and the adverse events requiring closest observation, at the top of each attached paper.

Conclusions

Psychiatric symptoms induced by IFN prevent patients from continuously receiving effective care and, in the worst-case scenario, cause suicide. It is necessary to carefully decide whether IFN is indicated or not for each patient, obtain informed consent based on full explanation, and administer IFN carefully.

Each patient and his/her family members should be asked whether they have any history of psychiatric symptoms before starting IFN. If any psychiatric symptom develops, it should be appropriately handled and carefully observed. It is necessary to inform family members of possible psychiatric symptoms in advance. It is useful to put consultation-liaison psychiatry with psychiatrists into clinical practice to prevent the progress of psychiatric symptoms and ensure appropriate action by medical teams.

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Radiocurable Tumors and Non-Radiocurable Tumors

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Abstract: In Japan, the main technique for curing patients with malignant tumors has been surgery. However, the rapid aging of the population has necessitated a change in treatment strategy, and radiotherapy has become a powerful option. The main concern with radiation therapy is its reliability, since some tumors are radiocurable whereas others are not. Although radiosensitivity was first reported in 1906 by Bergonie and Tribondeau, clinical radiocurability is somewhat different. Leukemias and lymphomas, while exceedingly radiosensitive, are not readily radiocurable. This article discusses recent progress in radiotherapy and other complementary treatments, including malignant lymphomas of the stomach, head and neck cancer, and lung cancer, with special emphasis on treatment success and QOL.

Key words: Radiocurable tumor; Radiosensitivity; Radiotherapy,; Malignant lymphoma; Head and neck cancer

Introduction

Japan currently is facing the effects of a rapidly aging population. Although it is fortunate that more and more people are living longer, this demographic change has created a number of problems as well. One problem specific to cancer treatment is that it has become more difficult to employ surgical resection as the primary treatment for malignant tumors. In addition, since more importance is being attached to the patient's quality of life, simply saving a patient's life is not necessarily the best option if severe limitations in subsequent daily living are apt to occur. Because of this, radiotherapy has been attracting increased attention. Radiotherapy, however, cannot be used as an alternative to surgical resection in every case because whereas some tumors are highly radiosensitive and thus responsive to radiotherapy, others are not.

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Radiosensitivity

Determination of the conditions for which radiotherapy is effective has been a major focus of attention almost since radiant rays were discovered. In 1906, only 11 years after the discovery of radiation, Bergonie and Tribondeau carried out an experiment in which irradiation to the testis of mice was used to determine the sensitivity of tissue. They found that the sensitivity of cells to radiation is proportional to the degree of proliferative activity and inversely proportional to the degree of differentiation. In other words, undifferentiated cells with high mitotic capability are more radiosensitive. According to this principle, tissues rich in actively dividing cells generally show high sensitivity to radiation, whereas those with few such cells have low radiosensitivity.

More specifically, genital glands such as the testis and ovary, lymphatic tissue, fetal tissue, and fetus-like blast cell tissue are highly radiosensitive. Tissues with low radiosensitivity include adult bone, fatty tissue, muscle, and large vessels. Because the radiosensitivity of a tumor reflects the sensitivity of the tissue from which it has arisen, malignant lymphomas, which originate in lymphatic tissue, and seminomas, which originate in the testis, have high sensitivity to radiation. In contrast, osteogenic sarcomas and liposarcomas demonstrate low radiosensitivity.

Epithelial tumors, or cancers in the narrow sense, are considered to have moderate radiosensitivity. Among these tumors, undifferentiated carcinoma and small cell carcinoma have relatively high radiosensitivity, followed by squamous cell carcinoma. The radiosensitivity of adenocarcinoma is generally lower than that of other types of epithelial tumors. In light of this, head and neck cancer, esophageal cancer, uterine cervical cancer, and skin cancer, among which squamous cell carcinoma is common, seem to be good indications for radiotherapy.

However, even among squamous cell carcinomas of the esophagus, some are highly radiosensitive but others are not. As this indicates, radiosensitivity depends not only on the histologic type of the tumor but also on other factors. The oxygen concentration in the tumor and the mitotic cycle of tumor cells are two such factors. For example, in tumors accompanied with ulcers or inflammation, tumor cells are in a hypoxic state, and thus respond poorly to radiation. Therefore, attempts to raise the oxygen concentration in tumor tissue, to develop drugs that increase the radiosensitivity of hypoxic tumor tissue alone, and to synchronize the cell cycle have been attempted, although the results so far have been unsatisfactory.

On the other hand, recent studies have clarified the DNA repair process and regulatory mechanism of cell death in radiation-injured cells. From these studies, the presence of cancer-related genes affecting the radiosensitivity of cells has become apparent. *p53* is a well-known cancer-related gene, as are *Bel-2* and *Fas*. In addition, other genes, including hepatoma-derived growth factor (HDGF),[1)] have been found as a result of differences in radiosensitivity among esophageal cancers. In recent years, angiogenetic factors such as vascular endothelial growth factor (VEGF) have been attracting attention in conjunction with radiosensitivity. The involvement of many other genes has been suggested, and the microarray technique, which allows simultaneous examination of these genes, has been an aid to research. Table 1 lists the factors involved in

Table 1 Factors Affecting Tumor Radiosensitivity

1. Histologic type
   - High sensitivity: Malignant lymphoma, Seminoma, etc.
   - Moderate sensitivity: Epithelial tumor (Carcinoma)
   - Low sensitivity: Osteosarcoma, Malignant melanoma, etc.
2. Oxygen concentration in tumor tissue: Radiosensitivity is low in the hypoxic state.
3. Cell cycle: Radiosensitivity is high in M phase and low in S phase.
4. Cancer-related genes: *p53*, *Bel-2*, *Fas*, VEGF, etc.

M phase: Mitotic phase, S phase: DNA synthetic phase.

the radiosensitivity of tumors.

In the clinical setting, however, gene diagnosis and the diagnosis of factors other than histologic type are not always feasible, and initiation of treatment may be necessary before the results of such diagnoses are available. Therefore, radiotherapy currently tends to be indicated for tumors of a highly radiosensitive histologic type, while attempts to increase the radiosensitivity of the tumor and concurrent treatment may be necessary for epithelial tumors of moderate radiosensitivity.

Some clinical examples of radiotherapy of tumors are described below.

Heavy particle therapy, which is not influenced by factors that affect radiosensitivity (e.g., hypoxic cells), and photon beam therapy, which affords minimal injury to normal tissue, have recently become available in Japan. However, these treatments are not common, and therefore will not be discussed here.

Malignant Lymphomas

Because malignant lymphomas are highly radiosensitive, radiotherapy was commonly employed for them in the past. However, non-Hodgkin lymphomas, which predominate in Japan, are likely to spread throughout the entire body, and, therefore, radiotherapy alone did not yield favorable therapeutic results because of frequent recurrence in non-irradiated areas. Effective anticancer drugs for malignant lymphomas, such as Adriamycin, were developed, and combination chemotherapy regimens were improved. In addition, adjuvant agents such as G-CSF began to be used, resulting in considerable improvement in the therapeutic results of malignant lymphomas. Subsequently, malignant lymphomas, particularly non-Hodgkin lymphomas, were treated for a time by chemotherapy alone.

However, in the latter half of the 1990s, randomized controlled studies[2] showed that short-term chemotherapy plus radiotherapy, rather than prolonged chemotherapy alone, achieved better results and was associated with fewer drug-related complications. The optimal combination of chemotherapy and radiotherapy to yield the best outcome is an important issue for the future.

Malignant lymphomas occurring in the stomach will be described briefly. The incidence of malignant lymphomas of the stomach is reported to be only about 1%, in contrast to gastric carcinomas. These lymphomas are divided into two types: mucosal-associated lymphoid tissue (MALT) lymphoma, which has lower malignancy, and usual diffuse B-cell lymphomas. Since MALT lymphoma is considered closely associated with *Helicobacter pylori*, patients with this disease are first treated by bacterial eradication using antibiotics. However, bacterial eradication is reported to be ineffective in 30% of patients with MALT lymphoma.

For cases of MALT lymphoma not amenable to bacterial eradication and those of diffuse lymphomas, gastrectomy was formerly the standard treatment, as in cases of gastric cancer. However, gastrectomy was associated with decreased quality of life mainly owing to postoperative dumping syndrome. To eliminate this drawback, treatment of malignant lymphomas of the stomach without gastrectomy was attempted through the cooperation of radiation oncologists from various institutions in Japan. More specifically, patients with MALT lymphoma were treated with radiotherapy alone when bacterial eradication was ineffective, while those with diffuse lymphomas were treated with a combination of chemotherapy and radiotherapy from the beginning, without eradication. Good therapeutic results were obtained in all 47 patients with gastric malignant lymphoma (22 with MALT lymphoma and 25 with diffuse lymphoma) without gastrectomy.[3]

Head and Neck Cancers

Most cancers occurring in the head and neck region are squamous cell carcinomas, which

often respond well to radiotherapy. However, radiotherapy in these cases may be less certain than surgical treatment.

Among laryngeal cancers, glottic cancer is clinically characterized by hoarse voice and, therefore, is often detected in stage I (T1N0M0) or II (T2N0M0). Radiotherapy has commonly been used for these cases with the aim of preserving the patient's voice. Formerly, local control of glottic laryngeal cancer in the T2 stage involving the laryngeal ventricle was not necessarily satisfactory after radiotherapy alone, with local control obtained in 70–80% of patients. In Kurume University Hospital, cooperation between head and neck surgeons and radiation oncologists resulted in a combination treatment by which part of the tumor is resected to allow greater preservation of voice quality, followed by irradiation to the reduced tumor. As a result, tumor control was achieved in more than 90% of patients without loss of voice quality.[4)]

Radiotherapy has been indicated for other cancers in the head and neck region that previously might have been subject to extensive surgical resection, owing to consideration of possible postoperative decreases in quality of life, including functional disturbances in swallowing and phonation as well as esthetic problems. Anticancer drugs were combined with radiotherapy to ensure efficacy of treatment.

Although concomitant anticancer drug therapy has been employed in various ways, we used direct periodic administration of anticancer drugs into the tumor via catheter from the femoral artery, applying an angiographic technique. Bolus intra-arterial administration of anticancer drugs into the tumor once weekly during radiotherapy is highly effective and is associated with minimal adverse effects and complications of anticancer therapy, since simultaneous systemic administration of antidotes to the anticancer drugs is possible through the venous route. Therefore, this rapid intra-arterial infusion of anticancer drugs is feasible for aged patients who are not amenable to systemic chemotherapy because of its adverse effects. For example, this technique has achieved favorable results in elderly patients with unresectable cancer in the sphenoidal sinus involving the cranial base and in those with advanced lingual cancer for which surgical treatment was denied. These patients have been followed to date without recurrence.[5)]

In Kurume University Hospital, selective rapid intra-arterial infusion via the femoral artery in combination with radiotherapy is employed for the treatment of maxillary sinus cancer, instead of continuous intra-arterial infusion from the superficial temporal artery. Selective rapid intra-arterial procedure has yielded excellent results, with fewer complications in comparison with infusion of anticancer drugs from the superficial temporal artery. Recently, some patients with maxillary sinus cancer have been admitted to a radiology clinic rather than a otorhinolaryngology clinic. Thus, a combination of radiotherapy and administration of anticancer drugs tailored to the specific patient can achieve tumor control even in cases not responding adequately to radiotherapy alone.

Not only anticancer drugs, but also hyperthermia may improve efficacy when combined with radiotherapy. Therefore, hyperthermia is also an option for combined treatment in suitable cases in Kurume University Hospital.

Lung Cancer

Lung cancer (specifically cancer of bronchoalveolar origin as used in this paper) ranks first as the cause of death among Japanese men. This type of cancer is often advanced when detected and therefore associated with very poor therapeutic results. Radiotherapy of lung cancer is usually inferior to surgical treatment in terms of certainty, and lung tissue is susceptible to radiation. Therefore, radiotherapy for this disease is used predominantly in patients in whom radical surgery is impossible or in whom control of symptoms caused by metastasis is

attempted. However, progress in diagnostic imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), have enabled accurate diagnosis of the properties and extent of the tumor even when it is still small. There have also been advances in technology for concentrating radiation on the tumor, such as stereotactic radiation therapy and intensity-modulated radiation therapy (IMRT), focusing high-dose concentrated radiation on the tumor alone, with minimal injury to the lung.

The use of these latest techniques in diagnosis and treatment can achieve therapeutic efficacy equal to or better than that of surgical resection, even in patients with adenocarcinoma, which is known to have relatively low sensitivity to radiation.[6] In the near future, the extension of these techniques is likely to offer treatment for lung cancer that maintains quality of life and eliminates the need for surgical resection.

Conclusion

Although various factors affect the radiosensitivity of tumors, histologic type is still an important indicator in clinical practice. In addition to tumors with a histologic type that is highly sensitive to radiation and thus responds well to radiation therapy, radiotherapy can be effective for tumors of a histologic type that has relatively low radiosensitivity and responds poorly to radiotherapy, provided that the mode of radiotherapy and type of combination therapy are carefully considered. Radiotherapy is expected to play an increasingly important role in the treatment of malignant tumors as Japan's population continues to age.

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The Globalization of Bioethics
—A review of current conditions in Japan for the health care system in the 21st century—

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Abstract: The concept of informed consent has not been accurately understood in Japan. Subsequently, this has resulted in the occasional breakdown of the physician-patient relationship at the clinical level. Bioethics, which is central to the concept of informed consent, has not taken root in Japanese culture, and this is the underlying cause for the lack of understanding. Unlike the doctrine of individualism that is practiced in the West, familialism and paternalism prevail in Japanese society. In addition to the physician, family members and other social environmental factors that surround the patient have also sustained paternalism. The opportunity for dialogue between the elderly and children has been lacking due to the aging population, the low birth rate, and the growing trend in nuclear families. The advent of problems stemming from the inability to imbue moral and ethical perspectives has become a social phenomenon; and this has impeded ethical contemplations about life. The great duty to the family and society has predominated as a virtue. As a result, Japan lacks the foundation that is needed to understand the meaning of patient autonomy. The time has come to delve into the process through which bioethics was established in the United States, to review the present state of our country, and to foster physician education, patient awareness, the importance of autonomy, and a global, moral perspective of the national populace.

Key words: Informed consent; Bioethics; Autonomy; Paternalism; Japanese national character

Introduction

The term, informed consent, was introduced to Japan quite some time ago. But, it has only recently begun to be seriously contemplated by physicians, patients, and their families from their respective viewpoints. This is probably due to the changes that have occurred in the

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health care environment. However, it appears that the practice of informed consent continues to precede public understanding in Japan. There is only a small minority of people who truly comprehend the spirit that underlies bioethics, as well as the fact that informed consent is a component of this broad doctrine.

Bioethics deals with all aspects of the phenomenon of life. It is based on established scientific knowledge. It is an academic discipline where fundamental ethics are debated; and it was mainly established in the United States.[1)] Informed consent was included as a protective measure in health care to safeguard the autonomy of patients. Thus, it is important to understand bioethics in its entirety, in order to practice informed consent. Help and cooperation in fostering general public understanding of bioethics through education and conventional public relation activities, as well as fostering a support system to enable the uncontrived introduction and practice of bioethics where physicians are trained will be demanded in the future of the health care community in Japan.

Relationship between Paternalism and the Japanese National Character

Familialism and paternalism are the national traits of Japan in contrast to the doctrine of individualism in the West. For example, if a person becomes ill in a country where individualism prevails, that person will think firstly about the treatment or other measures that he or she wants done and secondly, that person will consider the affect of their illness on family members and their employment. But, in the case of a Japanese individual, the majority will immediately worry about the inconvenience that their illness will impose on their family members and their jobs. In many cases, family members will accompany the individual to the hospital to receive an explanation about the illness. In decision-making scenarios, notably when the patient has to decide the type of treatment that will be carried out, patients commonly consult their spouses, parents, and siblings. In some instances, the patient's superior at the company will also be consulted.

In Japan, the perspective that an individual's existence is dependent on his family, home, and employment predominates. Additionally, the Japanese have been taught from childhood to seek the advice and supervision of parents, siblings, and superiors for major decisions that are made in their lives. Decisions that are not tolerated by an individual's elders tend to be seen as arrogant and are looked on with contempt. Thus, the lack of original thinking and the dearth of creativity that has been pointed out about the Japanese people are due to this mindset.

Individuals in Japan have been divested in large measure of the opportunity to exercise their autonomy. In the area of primary education, when children are told to "think for yourselves", many children become distressed because they are unable to come up with their own ideas. In advanced countries where bioethics is well established, the educational and social environment did not undergo reforms after the concept of bioethics was introduced. Rather, individuals have been constantly disciplined from childhood "to think for themselves when they have to make decisions". In other words, individualism as practiced in the West can be likened to a positive form of self-responsibility. This is also an important issue that affects individual perspectives about life and death.

Due to an aging population, low birth rate, and the continued growth of the nuclear family, communication between the elderly and children has diminished in Japan, and opportunities to reminisce about past events and experiences that teach moral values have declined. Likewise, the opportunity to witness the death of a family member at home has decreased. Job transfers to distant locations have become commonplace, and the vast majority of children do not witness the deathbed or the last moments of a parent. "Death" has become a

special phenomenon that is no longer experienced as part of daily life. The fact that death occurs to all human beings has been forgotten, and family members do not discuss the topic of death and dying within the family.

Subsequently, life and death perspectives are no longer grounded in reality. Thus, it is ambiguous as to whether patient autonomy truly reflects the will of the patient due to the assumptions that are held by family members when the need to make a decision arises. Consequently, the patient does not question the fact that there is no alternative other than to die under the care of the physician at the hospital. Despite the fact that this may be attributed to national character, the Japanese people appear to have unknowingly missed the opportunity to practice autonomy.

Paternalism is one of the keywords that describe the national character of this country. Paternalism exhibited by Japanese physicians when they take action "in the best interests of the patient" at the clinical level, is a form of warmhearted interventionism. Case in point, prior to explaining the condition of the disease to the patient, the physician will consult family members to ask what action they think should be taken. This is a typical example of paternalism. Informed consent, based on bioethics, is one of the rules that completely protect patient autonomy. Thus, the tradition of paternalism in Japan has impeded bioethics from taking root even among health care professionals. Moreover, there is a hidden predisposition to retain paternalism in this country.

This paternalism is occasionally strongly exhibited by family members. In the case of an adult patient with the intelligence and mental capacity to make decisions, the physician will generally disclose the name of the disease if requested by the patient. However, if the meaning of patient autonomy is not understood by the family, parents or other family members will be unyieldingly opposed to the disclosure of such information to the patient saying, "We don't want our child to know the name of the real disease because it's too cruel".

The parents remain immune to repeated explanations about the meaning of patient autonomy, its importance, and the dignity of an individual's life. Consequently, the patient's right to be informed is ignored. In order for the significance of autonomy and informed consent to take root in the Japanese society, the public needs to fully understand these terms before encountering the scenario of disease and illness. To accomplish this, the endeavor must be made to enable bioethics, which is the fundamental basis of autonomy and informed consent, to become firmly rooted in the Japanese society.

Opportunities to comprehend the meaning of autonomy must be increased as a matter of course in primary and secondary education and in family life. For the generation that has lived in an age when paternalism prevailed, effort must be made to change their awareness. Additionally, the health care environment must be improved to truly foster life and death perspectives as well as the ethics of the general public.

Historical Perspective of Bioethics

A brief history of bioethics shows that in tandem with the inhumane medical acts that were akin to human experiments which were conducted in the United States around 1960, the general public was galvanized to act in unison with lawyers, religious leaders, and ethicists to protect the rights of patients. Subsequently, issues, notably whether patient rights in health care were recognized, whether the autonomy of the patient was safeguarded in conjunction with the patient's acknowledgement of the risks that were involved, whether the medical action taken was lawful, whether the physician successfully executed his responsibilities were furiously contested in the courts of law.

The Nuremburg Code, which prohibits the atrocities conducted by the Nazis, was adopted as the first standard of ethics. The case of paternalism in patient absentia was detected in the Hippocratic Oath and criticized. The term,

informed consent, was established as a legal concept that evolved from efforts to verify if the decisions made by the patient were truly in accordance with the concept of autonomy.

Bioethics was conceived within this successful milieu, where it evolved and developed as an academic discipline that examined the overall phenomenon of life according to a code of ethics. Bioethics focused not only on health care, but widespread life issues such as life and death perspectives, prenatal diagnosis, genetic counseling, gender identity disorder, QOL, therapeutic trials, artificial insemination, gene diagnoses, which has recently become the focus of public attention, brain death, organ transplants, artificial organs, and genetic engineering. In tandem with the spread of bioethics, informed consent evolved beyond the bounds of one legal doctrine to encompass basic ethics where the overall decision-making process in health care and patient autonomy were truly considered. To protect the human rights or autonomy of the patient, informed consent is inseparable from the doctrine of bioethics.

The issues that confront Japan are clear. The concept of informed consent was introduced and accepted in our country without any pseudo experience remotely similar to the historical events that occurred in the United States. Subsequently, it has been accepted as simply another imported culturalism. Bioethics has been viewed as a special field of research, which has been ignored in medical education. Or perhaps Japan has been unable to perceive its significance. Irrespective of whether it is basic or clinical medicine, the content of the entire course of study for both medical and nursing students should be constantly ruminated and digested against the background of bioethics; and cross-sectional educational opportunities should be actively provided.

Distinction between Patient Egoism and Autonomy

Based on the above, it may be misconceived that the doctrine of individualism must be embraced in order to comprehend autonomy. The issue is not simply whether individualism is better. Misconceptions about individualism by patients who exhibit a one-sided, unilateral form of individualism are frequently seen at health care sites. In accordance with recent trends, patients are under the mistaken idea that they are able to "tell health care personnel what they want" because of their dominant position, and health professionals often encounter unreasonable demands by patients who are spurred on by a sense of their vested rights.

Recently, hospitals have become hypersensitive about the terms, service, and courtesy. Since the concept of "progressive health care" is extolled without fully comprehending the intrinsic nature of bioethics, hospitals have become overly reactive in their complete denial of the traditional pattern of "health care personnel are in dominance; and the patient is the vulnerable". There are frequent cases of hospitals that have become entangled in unreasonable and inconsistent claims over a lengthy period of time because of their desire to avoid a conflict. From the viewpoint of bioethics, the action taken by these hospitals is not always appropriate. Providing quality health care for the patient and providing a special environment for specific patients because the hospital has yielded to a certain type of pressure are two disparate situations.

The invasive medical or health care acts performed on a patient are justifiable only if the patient's consent has been given. This is an extremely important checkpoint in pursuing health and medical care. Protection from acts that are tantamount to illegal and injurious action is waived with the consent of the patient. In exchange, patients have the right to fully safeguard their autonomy or human rights. Despite a denial of the term, "vulnerable", if there are patients who make extreme demands by stressing their vulnerable status and believe it is the hospital's duty to provide everything the patient desires, this behavior is egoism and

not autonomy.

For example, a patient files a complaint that he is unable to park his car in the limited hospital parking area. He believes that he should be given priority parking because his disease is more acute than that in other patients, and he has been visiting the hospital for more than ten years. Due to the hospital's lack of an adequately sufficient parking area, many patients have undoubtedly been inconvenienced. However, this fact is external to the intrinsic essence of health and medical care. The medical care professional endeavors to provide health care services to the best of his abilities and tries to provide diagnosis and treatment that meet the needs of the patient. Despite the hospital's clearly worded statement that the hospital parking area was limited and its request that patients utilize public transportation, some patients continued to advocate their rights based on their beliefs described above. Such behavior by the patients is simply an act that ignores the hospital's policy and advanced notice to the patients about the parking situation. The patients who misinterpret the definition of their vested rights are often unable to establish an honest physician-patient relationship. Hence, implementing informed consent becomes naturally difficult.

Recently, the study of morals is no longer included in the curriculum of primary education in our country. Moral education is extremely useful in fostering ethical values, but when it is neglected in basic education, the fostering of a broad ethical perspective is impaired. At the family level, children adopt the most expedient means available to successfully navigate the "entrance examination hell" or competitive society since the tendency is for parents to evaluate their children solely on outcome, which is very problematic. This is equivalent to the perspective that "nobody matters except me". The general public must be educated that autonomy within the health care scenario is not an extension of egoism. Although patients have the right to exercise their autonomy, an environment must be created to promote their awareness that responsibility is generated in unison with this autonomy. The fundamental truth is that individualism and egoism are disparate, and autonomy and egoism are distinct. Hopefully, this basic ethical perspective will be fostered within the family and in primary education.

Difference between Paternalism and the Disclosure of Medical Information by the Physician

Informed consent exists to protect the rights of patients; and it is not a precursor to relieving the physician of stress in conducting medical treatment. Despite this fact, the misconception has been observed where informed consent, that consists of informing the patient of the disease name, providing an explanation of the benefits and disadvantages of the proposed treatment, and obtaining the agreement of the patient signifies full approval by the patient for all subsequent medical treatment. In addition, the argument that informing the patient of the disease is requisite in order to obtain the patient's informed consent is also problematic. The objective of informed consent is not simply to inform the patient of the specific name of the disease, but to obtain the patient's understanding by providing an explanation of the treatment and tests that are required in conjunction with the conditions of the disease, in order to enable the patient to understand the benefits and disadvantages of the treatment. The subsequent treatment measures are selected based on autonomy and patient approval. Two case examples, which demonstrate the difference, are given below.

Scenario 1

A patient is concerned about an abnormal result of liver function test. The physician tells the patient, "Let's do another examination just to make sure", and proceeds to make a reservation for a CT scan without ascertaining the

patient's intent. The patient, who feels that he must follow the doctor's instructions, reluctantly changes his work schedule and undergoes a CT scan. On the day the patient receives an explanation about the results of the scan, the physician says, "Mr. A, the CT scan shows that you have cancer of the liver. But it's in the early stage, so let's remove the cancer through surgery so that we can save your life. None of the patients at this hospital have died due to surgical accidents. I am going to give you a consent form for surgery. The form contains diverse details, but this is just a precautionary measure to inform you because of the occurrence of medical accidents elsewhere. There's nothing to worry about. If you decide to undergo the surgery, please sign the form and return it to me. Then I will make immediate arrangements for your hospitalization. If you are doubtful, you may go to another hospital for a second opinion, but any physician in Japan will tell you the same thing since the disease is so clear."

This physician feels that he has kindly explained the risks, the name of the disease, and made mention of the possibility of a second opinion. Therefore, he believes that the process of obtaining informed consent will have been satisfactorily carried out if the patient voluntarily signs the consent form.

Scenario 2

A patient is concerned about an abnormal result of liver function test. The physician tells the patient, "This type of numerical figure may be an indication of hepatitis, cirrhosis of the liver, liver tumor, or some other disease. Firstly, I would like you to take a CT scan to accurately diagnose the condition and then treat the disease. Is that all right with you? If you're willing, I can make reservation for tomorrow."

"Doctor, I thought that I might be able to take care of the condition through medication. But, based on your explanation, I'd like to undergo the CT scan. Please make the necessary arrangements. However, I'm busy at work tomorrow, so anytime after tomorrow is fine."

"All right, then how about 9:00 a.m. day after tomorrow?"

The patient undergoes the CT scan with a complete understanding of the situation. On the day he receives an explanation about the results of the scan, the physician says, "I'm also going to be looking at the film for the first time. I don't know what we'll find, but before I begin, I want to ask if you want to be told the specific name of the disease if we find something unpleasant including cancer. Or do you prefer that I explain the symptoms of the disease first, followed by the treatment that is available, and inform a family member designated by you about the name of the disease and details of the symptoms?"

The patient's wishes were, "Doctor, it's all right to tell me that it's cancer, as long as there's a chance of recovery. But if not, I think that the mental anguish will be too much for me. So don't tell me the specific name of the disease from the start. Just tell me what the symptoms are, what the best treatment is, and what will happen if I don't undergo the treatment. I'll have my wife come in to see you tomorrow. So please tell her everything."

"I understand... The film shows an abnormal shadow on your liver. I think that it's some kind of growth or a tumor. Tumors can be benign or malignant. But we don't have to determine this right now. The best treatment at this time is to surgically remove it. One other option is to insert a tube in the artery and cut off the blood supply to shrink the tumor, but this is not a complete cure. Another option is to use drugs, but they are not very effective from my experience, so I don't recommend this method at the hospital. However, since the tumor is the reason for the abnormal test value, it will deteriorate and develop into a complex disease if it remains untreated. Based on our past experience, there is a high possibility for a complete cure when a tumor of this size is removed surgically. If you wish, I can discuss the type of tumor you have after it is surgically removed

and pathologically diagnosed accurately. It's better not to worry too much at this stage. If you decide on surgery, your consent will be based on an understanding of the general risks associated with surgery. I will explain the disease and the benefits and disadvantages of each treatment method in detail to your wife tomorrow. Please discuss the subject with your wife at home and sign and return this form after you have fully understood everything. If there is anything that you do not understand, I will answer your questions as many times as needed. If you should change your mind at any time, we will take action according to your wishes. If there is another physician whom you wish to consult, please go ahead and get a second opinion. I will lend out your CT scan at anytime."

Despite this explanation, the physician was concerned that he had raised the fears of the patient about cancer. The next day during the consultation meeting with the patient's wife, he informed her that her husband did not want to be told the name of the disease at this point in time, but that should her husband change his mind later, he would be willing to explain the disease again. He also discussed the possibility of the need to provide mental support for her husband.

Patients have the right to know as well as the right not to know the disease that they have. This is an important point in informed consent. The misconception prevails that the most difficult aspect to obtaining informed consent is informing the patient about the name of a malignant disease; and there is a tendency to pursue this line of thinking by a segment of health professionals. But as attested to in the chapter dedicated to "communicating negative information to patients" in textbooks on bioethics, such information must be broached to the patient very carefully. Scenario 1 above depicts a typical case of physician paternalism and mistaken conviction. Scenario 2 is a good example about the process through which informed consent should be obtained.

But, supposing the liver tumor was in fact liver cancer and the patient was falsely told it was liver hemangioma in Scenario 2. If the patient decided to go through the flood of medical information available because he doubted the physician's explanation and began to realize that the disease hemangioma did not fit his symptoms, the physician would be seen with great suspicion by the patient and his family. When the situation devolves to this point, the physician-patient relationship is shattered. Not only is informed consent no longer achievable, but the patient will also suffer emotional anguish stemming from the knowledge that the name of another disease was given falsely in order to hide the truth. Subsequently, the patient would experience an emotional shock just as great in impact as if he had been told that he had cancer.

On the premise that the patient's complete understanding is achieved, the various treatment options provided by the physician that are available to a patient and an explanation of the risks involved are just as equally important as the patient's right to know and the right not to know the disease that he has. In providing the treatment options that are available, it is acceptable for the physician to explain which option has the highest degree of reliability. But irrespective of whether the prerequisite is for surgery, the manner in which the physician makes his recommendations should not interfere with the patient's ability to make the decision freely. The physician should not become unkind or offended because the patient did not select the treatment that he personally wanted for the patient. If a physician strongly believes that the second and third treatment options are not favorable, he must thoroughly and clearly explain the risks based on fact and provide the patient with adequate information to allow him to make the right decision.

Irrespective of whether the physician approves of the patient's choice of treatment or not (informed choice), the physician is obligated to reiterate the risks involved and to

ascertain that the patient clearly understands them when he makes his decision (informed decision). The patient agrees to allow the physician to perform the treatment and to request it formally (informed consent). It is important that these steps are followed in obtaining informed consent.[3)]

The greatest concern of the patient is to regain the QOL that has been lost in the endeavor to overcome the disease. But health care professionals have tended to subject patients to a presupposed concept of QOL, and the extent to which it is achieved has been evaluated against this concept. This is also a form of paternalism that is exhibited by health care professionals. It is important to allow the patient to determine what the optimum state of QOL is for that patient. An evaluation of QOL becomes meaningful only if the degree to which QOL has been achieved is measured in terms of the goals set by the patient.[4,5)]

Within the milieu of the physician-patient relationship — from communication beginning with the initial diagnosis, the significance of general tests, drug prescriptions, an explanation of the medication currently taken by the patient, to counseling on future diagnoses and treatment — there exists a variety of situations dealing with informed consent.[6)] The physician will be required to adjust his manner of communication and the way in which he presents his recommendations according to the individual personality of the patient, and thereby, build the groundwork where informed consent can be achieved.[7)] At each stage of the physician-patient relationship, the autonomy of the patient must be ascertained. Constant awareness of this fact will help keep the physician from becoming stereotyped in his attitude and to contemplate physician-patient relations from an ethical standpoint.

Prior to fostering interview and diagnostic skills at the medical education level, it is important to create an environment where the ability to view the situation from the patient's standpoint is fostered. Early exposure by medical and nursing students during their beginning years of study (prior to acquiring medical knowledge, students are made to experience health care with a patient at health and medical care sites) will help them to become aware of the meaning of QOL from the patient's viewpoint and to concretely experience autonomy. This method is expected to become widely utilized.[8)]

Fostering Autonomy through Education and Living Environment

The concept of bioethics is extremely broad. Subsequently, physicians experience and practice only a segment of this concept at actual medical and health care sites. In Japan, where many physicians presently view informed consent as a special ritual, proper health care that safeguards the autonomy of the patient cannot be achieved. This is due in part to the physicians' lack of awareness, their inability to put informed consent into practice, and the absence of a disposition based on their good faith as human beings, as well as the patients' lack of an accurate understanding of the meaning of autonomy. This fact has created the "I leave it up to you" patient mindset in health care, compounded by the paternalism that is retained by health care professionals and the tendency to shift to an egoism that emphasizes an excessive consciousness of patient rights. When the physician is unable to cope with the situation according to an appropriate ethical perspective, the direction of health care tilts toward the wrong side.

A flexible attitude is needed to cope with a generation of patients, notably the elderly, who are unable to follow in the wake of changes that have occurred in health care. If the physician is told by such patients that "I leave the decisions up to you," it is his responsibility to examine why the patient has responded in this way and to try to draw out the inherent autonomy.[9,10)]

The health care professional must pursue

this matter with strong convictions. There is a tendency for patients, who do not face autonomous decisions such as life or death surgery, to believe that they do not have the opportunity to practice informed consent. But the physician who provides guidance on improving the life habits or drawing out the voluntary volition of an outpatient with a mild chronic disease will probably constantly have the issue of informed consent in mind during diagnosis and treatment of the patient.[5,11)]

Medical and health care information acquired from textbooks is a comprehensive compilation of knowledge and technology. But an overemphasis of this fact has diminished opportunities for the physician to lend an ear to the innermost desires of the patient and to ask himself what is in the best interests of the patient from the patient's standpoint. It is self-evident that the diversity of troubles and incidents in the field of medical and health care due to the dehumanization of patients throughout the country stem from the prioritization of knowledge and technology during the stage when young physicians are fostered.

Under the premise that "All human beings make mistakes. That's why a system must be created to prevent them before they occur," attempts are being pursued to utilize risk management to resolve the variety of incidents that have occurred at medical and health care sites. A review as to whether informed consent was obtained becomes important, and if dissatisfaction or suspicion stemming from a discrepancy in sensitivities or from physician-patient relations exists, it should be seen as a bioethics related incident. To resolve such incidents, an environment that will allow an investigation that is based on an appropriate ethical perspective must be established.

Moral education of the national populace, ethical values in education, and the environment must be reviewed. Opportunities to contemplate the sacredness of life should be increased and a variety of opportunities to discuss life's preciousness and the need to safeguard one's own life should be provided during primary education or in family life. It may be necessary to pursue repeated public relations activities or utilize the broadcasting media to create such opportunities. There is high public interest in the news coverage of reproductive health care, organ transplant, and other aspects of advanced medical technology. Taking advantage of this public interest, news coverage that includes information about bioethics or other measures such as public debates about life and death issues by lawyers, religious leaders, philosophers, members of the general public as well as physicians and scientists that will help the widespread dissemination of bioethics should be pursued.

In the field of bioethics, where Japan has begun to lag, good health care, relevant health care, and patient centered health care will be achieved when informed consent based on bioethics is properly implemented. To achieve this on a widespread scale is, in truth, the foremost goal of the 21st century health care in Japan.

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DRG/PPS

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Abstract: A trial project to introduce a Japanese version of the diagnostic related group/prospective payment system (DRG/PPS) was conducted at ten national hospitals from November 1998. However, many problems have surfaced—foremost among them were incomplete DRG classifications, inadequate reviews of payment amounts that simply reflected the past performance of the hospitals, and incomplete databases that lacked information on complications and other key components. In Japan, where documentation of patient data including discharge summaries is inadequate, one means of improving the existing situation is to emulate Europe, where the DRG is used as an indicator to help determine the budget for hospitals. However, even in such cases it should be limited to tertiary hospitals where database development and medical record audits are more easily achieved.

Key words: DRG; PPS; Standardization; Database; Discharge summary

What is DRG/PPS?

Diagnostic Related Groups (DRG) is a patient classification system that categorizes patients into groups according to clinical diagnoses, surgical procedures and financial criteria, notably hospitalization costs. Patients are classified into four levels. In Level 1, patients are grouped according to major disease categories. In Level 2, patients are categorized according to the use or non-use of surgery; in Level 3, patients are grouped according to diagnoses in the case of internal medicine or surgical procedure in the case of surgery; and in Level 4, patients are grouped according to the existence or absence of morbidity or complications and age. The total number of groups is about 500. An example that shows the levels for ophthalmology is given in Fig. 1.

The prospective payment system (PPS) determines the inclusive payment per hospitalization for each DRG. In the case of a patient who has been grouped into the appendectomy DRG, a fixed hospitalization fee for this DRG is paid, regardless of the length of hospitalization or the cost of the drugs used. However, the actual payment varies according to the price-wage level of that region as well as the number of residents-in-training. In the United States, patients are reimbursed for medical costs according to the DRG/PPS by Medicare (health insurance for the elderly and the disabled). But in Europe,

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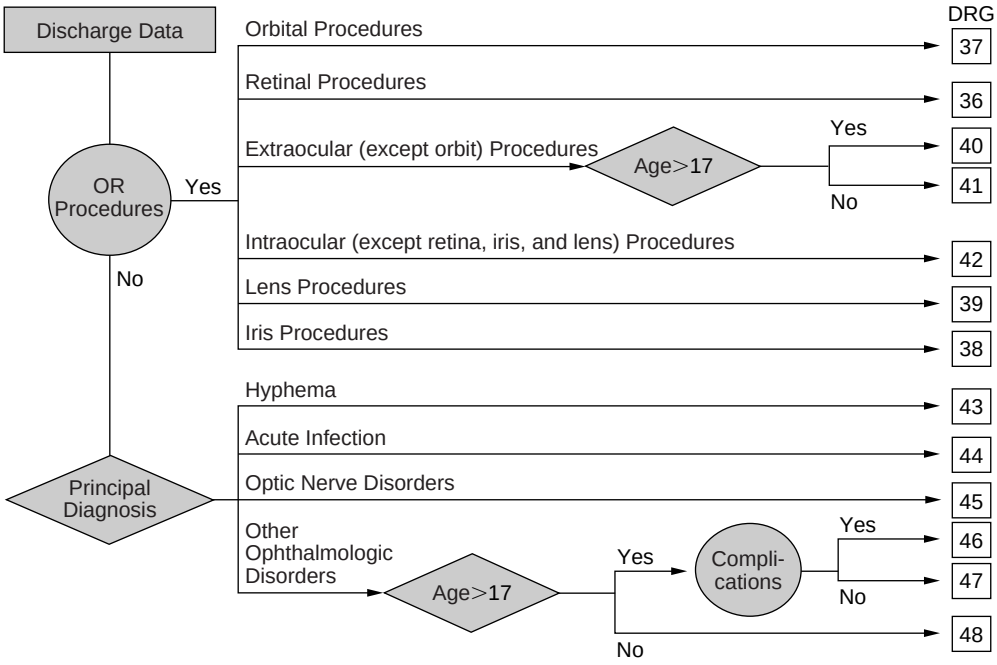

Fig. 1 Flow of DRG grouping (ophthalmology)

the DRG, which is separate from the PPS, is used as an indicator to determine the budget of each hospital. In addition, physician fees are not included in the United States, but they are included in Europe.

Historical Background of DRG/PPS

Prior to the introduction of the DRG/PPS in the United States in 1983, the federal government did not regulate the medical payment system as in Japan. Insurance companies reimbursed the medical costs of patients for the amount that hospitals billed for their services. As a result, Medicare faced a financial crisis; and the amount billed for patients who underwent similar medical care varied considerably between hospitals.

The DRG/PPS method was implemented on a trial basis in the state of New Jersey. Consequently, it was adopted by the federal government when initial concerns such as cost disparities between hospitals and increased readmission ratios did not occur. The DRG was originally developed to compare patient costs generated at each hospital. Thus, utilizing the DRG as an indicator to determine hospital budgets, as in the case of Europe, is more reflective of its original objectives.

Implementing the DRG/PPS

Following the adoption of the DRG/PPS in the U.S. health care system, firstly, the average number of hospitalized days decreased. If a patient was hospitalized longer than the standard number of days set for the DRG, the hospital faced a deficit. In contrast, if the patient was discharged earlier, the hospital profited. In addition, in the United States, the amount of PPS payments made for each DRG was adjusted according to the performance report containing the number of hospitalized days. Thus, the number of hospitalized days tended to be reduced with each revision. This phenomenon is similar to the spiraling decrease in the reimbursement for drugs, reflecting market prices that has occurred in Japan.

Secondly, hospital admissions were reduced, and the hospital occupancy ratio dropped to 60 percent, while the hospitalization of seriously ill patients rose. As a result, hospital wards fulfill the role of ICUs in Japan. Patients, who would have been hospitalized in the past, have come to be treated at outpatient clinics or forced to rely on home health care agencies or nursing homes. In addition, the majority of surgeries have become one-day surgeries carried out at outpatient clinics, and the condition of patients receiving home health care or placed in nursing homes has worsened. Due to this transition, although hospitalization costs were reduced, overall health costs have not necessarily been contained.

Thirdly, due to the fixed and all-inclusive PPS reimbursements for each DRG, the need to maintain the quality of patient care within the PPS framework has facilitated the standardization of health care, notably through clinical pathways. In addition, hospitals have become more careful about reporting the diagnoses and surgical procedures that they provided since their revenue has become dependent on this information. The medical record audit system has also become more strict to ensure that the DRG coding is accurate.

International Trends and the Situation in Japan

The DRG in Europe is utilized as one indicator to measure the efficiency of hospitals and the disparities in costs between health care facilities for regional health care plan purposes. In Korea, the scope of the DRG/PPS has gradually expanded from appendectomies and hernias. Initially, the hospitals opposed the introduction of this system, but it was eventually accepted because it proved to be more profitable.

A Japanese version of the DRG was implemented in Japan on a trial basis at ten national hospitals from November 1998. However, several problems became evident during this trial project. Firstly, the classification system was incomplete and more than 30 percent of the patients could not be categorized. Secondly, the points given to each DRG were based on the existing rates of the fee-for-service payment system. Neither the appropriateness of the health care service nor the cost was reviewed. For example, in the case of cataract surgery for one eye, the average hospitalization period is fixed at 8.5 days or 21,618 points (excluding the surgery), which is clearly an overpayment given the fact that one-day surgeries have become commonplace. Thirdly, the points given for complications in acute bronchitis, degenerative osteoarthritis, and bladder cancer were lower than in cases without complications because the comorbidity information was not recorded accurately.

Therefore, the existing conditions at other hospitals should be investigated before expanding the trial program. Although final diagnoses are essential for the DRG system, only 40 percent of all hospitals prepare discharge summaries. Furthermore, recalculating the charges for each admission from the claims that are submitted on a calendar month basis is not an easy task.

Impact on Future Health Care

The introduction of the DRG/PPS in Japan will have a significant impact on achieving the standardization of health care and reducing the average number of hospitalized days. However, in view of the existing situation in Japan, one method is to utilize the DRG to establish hospital budgets as is the case in Europe, but for only tertiary hospitals where database development and medical record audits are easier to undertake.

Effective Intervention for Smoking Cessation

—Practical guidance for medical facilities including smoking cessation clinics—

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Abstract: The essential of tobacco use is nicotine dependence. It is important to understand that habitual smoking is a chronic dependency that is liable to relapse but is amenable to repeated treatment, and to incorporate the treatment of this dependency into the routine healthcare activities. The efficacy of therapeutic programs that deal with smoking cessation on the basis of approaches using behavioral science and pharmacology has been established, and it is apparent that the cost-effectiveness of such treatment is extremely high among the various healthcare programs available. This paper introduces a therapeutic approach (the "5 A's") that can be implemented within a short period of time at outpatient clinics and discusses the use of nicotine replacement therapy.

Key words: Smoking cessation; Nicotine replacement therapy; The "5 A's"; Smoking cessation clinic

Introduction

Tobacco has not always been recognized as an addictive substance, with claims having been made that there is no obvious physical dependence and that tobacco use does little harm to society. However, a number of recent studies have demonstrated the mental and physical dependence resulting from tobacco use, leading to general acceptance of the view that it is one of drug abuses. In Western countries, there has been a movement to deal with the treatment of nicotine dependence as part of routine healthcare activities, with the understanding that this condition is "a chronic disease which is liable to relapse, but can be cured by repeated treatment."

Thus, smoking cessation intervention is a treatment for nicotine dependence and represents a type of health service from which pre-

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ventive and prognostic benefit for various diseases related to smoking can be expected. Moreover, smoking cessation intervention can be regarded as a high-priority service in light of its extremely high cost-effectiveness relative to many health services.

Because the medical milieu is an environment in which many tobacco smokers are encountered, it is a good setting in which to provide smoking cessation intervention. If healthcare professionals were to provide such intervention to smokers as part of their routine procedures in the treatment of patients or in general health examinations, society as a whole would benefit from a reduced number of smokers even if the success rate of smoking cessation is not so high.

According the results of a meta-analysis of about 300 randomized controlled trials concerning smoking cessation,[1] a clinician's advice to a general patient to stop smoking is effective even if it is as brief as 3 minutes. The percentage of smokers abstinent for 6 months or more was 2% higher when advice was given than when it was not. In addition, brief advice (up to 10 min) plus nicotine replacement therapy increased the corresponding abstinence rate by 9% as compared with no intervention. It has also been reported that a team approach involving physicians and other medical staffs increases the abstinence rate.

This paper describes methods of assisting smokers in overcoming their nicotine dependence and is aimed at those who work in clinical practice at general outpatient clinics or specialized outpatient clinics for tobacco dependence. Also included is a discussion of the effective use of nicotine replacement therapy.

Methods and Practical Aspects of Facilitating Smoking Cessation at Outpatient Clinics

This section introduces the therapeutic approach that employs the "5 A's" (Ask, Advise, Assess, Assist, Arrange) (Table 1), which is commonly adopted in major guidelines on smoking cessation in the UK and US.[2] The "5 A's" method is well suited to a brief intervention for smoking cessation at outpatient clinic.

In the first step (Ask), the procedure is to implement an office-wide system which ensures that, for every patient at every clinic visit, tobacco-use status is asked and documented in order to assure the systematic screening of all patients for smoking cessation intervention. For this purpose, the guidelines recommend expanding the entries of vital signs to include tobacco use or the use of an identification system, such as placing tobacco-use status stickers on all patient charts.

In Step 2 (Advise), the procedure is to urge every tobacco user to quit, in a "clear, strong, and personalized" manner. Physicians and other healthcare professionals should be careful not to offer vague messages of smoking cessation, such as "it's better to quit smoking if possible" or "try to cut down if it doesn't seem possible for you to quit". These statements weaken the motivation of patients to quit smoking. The "strong" manner referred to here means in such a way that emphasizes the high priority of quitting smoking as a task for the patient to deal with.

The procedure in Step 3 (Assess) is to ask every tobacco user if he or she is willing to make a quit attempt at this time. If the patient is willing to do so, specific support (Steps 4 and 5) should be provided. If the patient is unwilling to make a quit attempt, motivational intervention such as that shown in Table 2 should be provided.

The procedure in Step 4 (Assist) is to aid the patient who is willing to make a quit attempt (1) by helping him or her to formulate a quit plan to set up a quit date and providing advice on how to prepare for quitting (creating an environment suitable for quitting, including asking for support from others; developing a perspective on nicotine withdrawal symptoms), (2) by providing practical counseling (concerning the clinical importance of total abstinence;

Table 1 Brief Strategies to Help the Patient Willing to Quit Tobacco Use—The "5 A's"

Step	Strategies for implementation
Step 1: Ask (systematically identify all tobacco users at every visit)	· Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented. · Expand the entries of vital signs (blood pressure, pulse, weight, etc.) to include tobacco use (current, former, never) or use an alternative universal identification system (e.g., placing tobacco-use status stickers on all patient charts).
Step 2: Advise (Strongly urge all tobacco users to quit (in a clear, strong, and personalized manner))	Advice should be: · Clear: "I think it is important for you to quit smoking now and I can help you." "Cutting down while you are ill is not enough." · Strong: "As your clinician, I want you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. The clinic staff and I will help you." · Personalized: Tie tobacco use to current health/illness, and/or its social and economic costs, motivation level/readiness to quit, and/or the impact of tobacco use on children and others in the household.
Step 3: Assess (determine willingness to make a quit attempt)	· Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days). If the patient is willing to make a quit attempt at this time, provide assistance. If the patient is unwilling to make a quit attempt at this time, provide a motivational intervention.
Step 4: Assist (aid the patient in quitting) • Help the patient with a quit plan.	A patient's preparations for quitting: · Set a quit date (ideally, the quit date should be within 2 weeks). · Tell family, friends, and coworkers about quitting and request understanding and support. · Anticipate challenges to planned quit attempt, particularly during the critical first few weeks. These include nicotine withdrawal symptoms. · Remove tobacco products from your environment. Prior to quitting, avoid smoking in places where you spend a lot of time (e.g., work, home, car).
• Provide practical counseling (problem solving/skills training).	· Abstinence: Total abstinence is essential. "Not even a single puff after the quit date." · Past quit experience: Identify what helped and what hurt in previous quit attempts. · Anticipate triggers or challenges in upcoming attempt: Discuss challenges/triggers and how patient will successfully overcome them. · Alcohol: Since alcohol can cause relapse, the patient should consider limiting/abstaining from alcohol while quitting. · Other smokers in the household — Quitting is more difficult when there is another smoker in the household. Patients should encourage housemates to quit with them or not smoke in their presence.
• Provide intra-treatment social support.	· Provide a supportive clinical environment while encouraging the patient in his or her quit attempt. "My office staff and I are available to assist you."
• Help patient obtain extra-treatment social support.	· Help patient develop social support for his or her quit attempt in his or her environments outside of treatment. "Ask your spouse/partner, friends, and coworkers to support you in your quit attempt."
• Recommend the use of approved pharmacotherapy, except in special circumstances.	· Recommend the use of pharmacotherapies found to be effective. Explain how these medications increase smoking cessation success and reduce withdrawal symptoms. The first-line pharmacotherapy medications include: sustained-release bupropion hydrochloride (not approved in Japan), nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch.
• Provide supplementary materials.	· Provide supplementary materials appropriate for the patient (Sources—Governmental agencies, nonprofit agencies, or local/state health departments).
Step 5: Arrange (Schedule followup contact)	· Timing: Followup contact should occur soon after the quit date, preferably during the first week. A second followup contact is recommended within the first month. Schedule further followup contacts as indicated. · Actions during followup contact: Congratulate success. If tobacco use has occurred, review circumstances and elicit recommitment to total abstinence. Remind patient that a lapse can be used as a learning experience. Identify problems already encountered and anticipate challenges in the immediate future. · Assess pharmacotherapy use and problems. Consider use or referral to more intensive treatment.

(AHRQ: The Agency for Healthcare Research and Quality, 2000)

Table 2 Brief Strategies to Enhance Motivation to Quit Tobacco Use—The "5 R's"

Relevance	Encourage the patient to indicate why quitting is personally relevant, being as specific as possible. Motivational information has the greatest impact if it is relevant to a patient's disease status or risk, family or social situation (e.g., having children in the home), health concerns, age, gender, and other important patient characteristics (e.g., prior quitting experience, personal barriers to cessation).
Risks	The clinician should ask the patient to identify potential negative consequences of tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient.
Rewards	The clinician should ask the patient to identify potential benefits of stopping tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient.
Road blocks	The clinician should ask the patient to identify barriers or impediments to quitting and note elements of treatment (problem solving, pharmacotherapy) that could address barriers.
Repetition	The motivational intervention should be repeated every time an unmotivated patient visits the clinic setting.

(AHRQ, 2000)

limiting or abstaining from alcohol particularly immediately after the quit date; learning how to deal with other smokers, if any, in the household; identifying what interfered with previous quit attempts and providing advice on how to succeed), (3) by providing advice about the use of social support (concerning the use of support from healthcare professionals, family, friends, and coworkers), (4) by implementing pharmacotherapy, and (5) by providing supplementary educational materials on smoking cessation.

In Step 5 (Arrange), the procedure is to schedule follow-up contact for the patient with a quit plan to help him or her succeed in the quit attempt. It is recommended that the first follow-up contact occur soon after the quit date, preferably within the first week, and that a second follow-up contact take place within the first month. Congratulating the patient on his or her sustained abstinence provides great encouragement.

Role and Practical Aspects of Specialized Smoking Cessation Clinics

The role of outpatient clinics that specialize in helping patients overcome nicotine dependence is to provide special treatment to patients for whom brief intervention at a general outpatient clinic is insufficient to produce successful abstinence. Nicotine gum and the nicotine patch were introduced as a prescription drug to Japan in 1994 and 1999, respectively. As a result of these opportunities, an increasing number of outpatient clinics that specialize in treating nicotine dependence have been set up. A total of 247 institutions in this country as of January 2002 have such clinics (a list of outpatient clinics specializing in nicotine dependence in Japan is available at the URL of the Osaka Medical Center for Health Science and Promotion: http://www.kenkoukagaku.jp).

We opened a clinic specializing in the treatment of nicotine dependence in the Osaka Cancer Prevention and Detection Center in October 1998, and are continuing to treat patients in the clinic, which moved to the Osaka Medical Center for Health Science and Promotion in July 2001. More than 1,500 smokers have visited our clinic to date. In this clinic, a physician and counselor team is assigned to a particular patient, and methodology based on the results of research in two scientific fields, behavioral science and drug dependence, is used. A flowchart of the initial and subsequent visits to the clinic is shown in Fig. 1. The patient is interviewed individually for about 1 hour at the time of the first visit and for about 30–40 minutes at

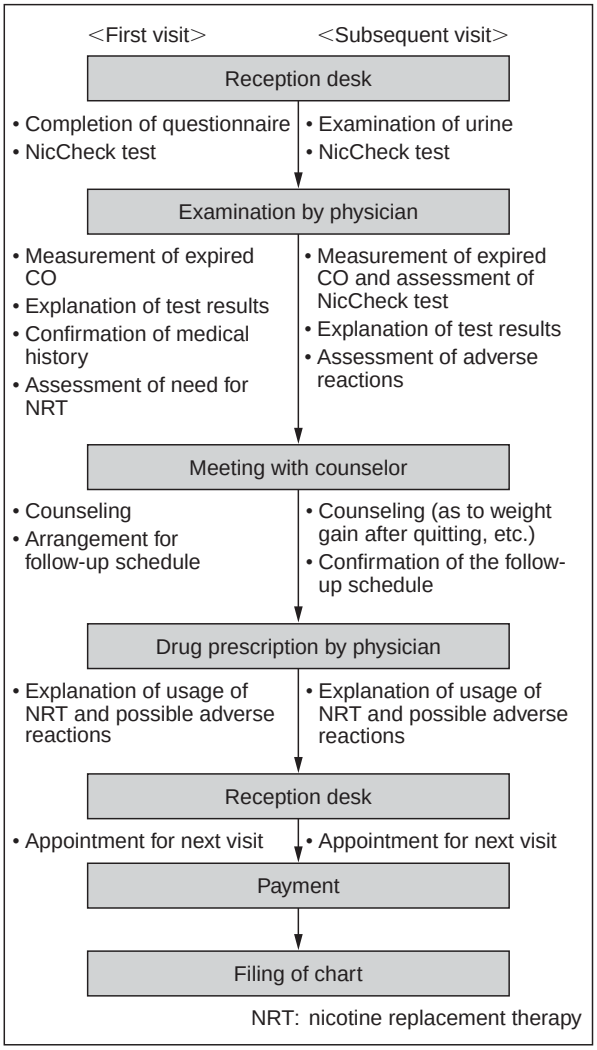

Fig. 1 Flowchart of treatment in the specialized smoking cessation clinic of the Osaka Medical Center for Health Science and Promotion

subsequent visits.

Patient visits to the clinic are scheduled using an appointment system, with the date of visits scheduled at times convenient for the patient. Most patients attend the clinic once every 2–3 weeks during the first few months after the quit date, because they usually use nicotine replacement therapy and therefore require assessment of its efficacy and possible adverse reactions as well as additional prescriptions at such intervals. The frequency of visits decreases to once every 1–2 months after three months of abstinence, when prescriptions for nicotine replacement therapy are generally terminated. In this clinic, patients "graduate" when abstinence from smoking has been maintained for 6 months from the quit date. On the day of the graduation ceremony, a photograph of the patient together with the physician and counselor is taken and placed on the certificate of course completion. This certificate is given to the patient to encourage continued abstinence.

Table 3 Meta-Analysis of Studies on the Efficacy of Nicotine Replacement Therapy

Nicotine replacement therapy (No. of trials)		Quit rate odds ratio (95% CI)
Gum	(48)	1.63 (1.49–1.79)
Patch	(31)	1.75 (1.57–1.94)
Intranasal spray	(4)	2.27 (1.61–3.20)
Inhaler	(4)	2.08 (1.43–3.04)
Sublingual tablet	(2)	1.73 (1.07–2.80)
All formulations		1.71 (1.60–1.83)

(Lancaster, 2000)

Pharmacotherapy for Nicotine Dependence—Nicotine Replacement Therapy

Various drugs have been examined as pharmacotherapy for nicotine dependence. Among them, nicotine replacement therapy has been established as safe and efficacious and is in widespread use throughout the world.

Nicotine replacement therapy using chewing gum or other formulations of nicotine supplies the patient with nicotine to relieve the withdrawal symptoms that occur during abstinence. With this therapy, the patient initially is weaned from psychological dependence, then from physical dependence through adjustment of the nicotine supply. According to a meta-analysis of studies on the effect of nicotine replacement therapy carried out in various countries, the therapy increased the chances of quitting 1.7-fold in comparison with placebo, as shown in Table 3.[3)]

Table 4 Characteristic Features of Nicotine Gum and Patch

	Nicotine gum	Nicotine patch
Advantages	1. Allows self-regulation of the nicotine dose. 2. Is short-acting. 3. Offers both oral and tactile gratification.	1. Easy to use. 2. Allows maintenance of stable nicotine concentrations in blood.
Disadvantages	1. Requires instructions on proper use. 2. May cause nausea and irritation of the mouth and throat.	1. Cannot handle abrupt surges of craving. 2. May cause skin reddening or rash, and sleep disorder.

In Japan, chewing gum and patches are the currently available formulations of nicotine replacement therapy. The greatest merit of the nicotine patch is that it provides stable blood concentrations of nicotine when renewed every morning. On the other hand, nicotine gum is advantageous in that it provides a more rapid increase in the nicotine concentration in blood than the nicotine patch, so that it can better handle abrupt surges of craving for tobacco. Based on the characteristic features of these two formulations (Table 4), our clinic uses the nicotine patch as the basic formulation, and adds nicotine gum as supplementary dosing for surges of craving or for times when the effect of the nicotine patch is not adequate in the morning. In addition, we recommend concomitant use of nicotine gum for patients in whom the nicotine patch with the highest dose of nicotine (Nicotinel TTS30®) is considered to be insufficient. In selecting the dose of the nicotine patch, it is convenient to use a color test paper, NicCheck [Dynagen Inc., USA], which allows semi-quantitative measurement (0–14, 15 levels) of nicotine and its metabolites in urine. According to data from patients in our clinic who used the patch for 7 consecutive days without smoking, Nicotinel TTS30® (nicotine content 52.5 mg) provides a 4.8 ± 1.3 (mean $\pm$ standard deviation) NicCheck level of nicotine, TTS20® provides a 3.4 ± 1.4 level, and TTS10® provides a 1.8 ± 0.7 level.[4] When the nicotine patch is prescribed to the patient at the first examination, these data are used as a yardstick, based on the NicCheck level determined.

In Japan, nicotine gum was formerly a prescription drug that was not covered under national health insurance. However, it was approved as an over-the-counter drug in June 2001, and has been available in drugstores since September 2001. Readers are referred to two of the author's papers for detailed usage of the nicotine patch and nicotine gum.[5,6]

Conclusion

Although tobacco epidemic became prevalent in Japan about 30 years later than in the West, its epidemic was substantial by the 1970s, and Japan currently has the highest level of tobacco consumption among the developed countries. It is therefore easy to predict that health hazards caused by tobacco use will become a serious social problem as the population ages.

Nicotine dependence treatment is an anti-smoking measure that can be implemented by healthcare professionals in routine clinical settings. The efficacy and cost-effectiveness of such intervention have been demonstrated by scientific evidence, and it is expected to have greater immediate effects on reducing smoking prevalence than smoking prevention. Health hazards caused by tobacco use in the first half of the 21st century occur mainly in those who are current smokers. Therefore, comprehensive anti-smoking measures, including nicotine dependence treatment, are urgently needed.

We have developed educational materials for medical institutions and healthcare profes-

♦ Osaka Prefecture's guidelines for tobacco control (for medical institutions) [digest edition]

In May 2000, the Osaka Prefectural government developed guidelines to curtail tobacco use in medical institutions, with the goal of achieving the smoking ban or complete isolation of smokers in specified areas and providing support for smoking cessation in all medical institutions by 2005. The guidelines propose specific activities for this purpose.

●Osaka Prefecture's guidelines for tobacco control (for medical institutions) [digest edition]

♦ Educational materials useful for the support of smoking cessation

Material that allows medical institutions to self-assess the extent of their support for smoking cessation is available as well as various other materials including an instructor's manual describing how to provide support and leaflets to patients.

●Checking smoking cessation support activities
"What is the level of preparedness and achievement in your institution?"

●Smoking cessation support: instructor's manual

♦ Educational materials useful for promoting the smoking ban or isolation of smoking in medical institutions

A pamphlet is available that allows individual medical institutions to self-assess their progress in smoking ban or isolating smoking in the institution.
Also available is illustrated material that introduces important points in promoting the smoking ban or isolation of smoking, specific practical procedures, and successful examples.

●Checking smoking restriction in medical institution
"Is your institution progressing with the isolation of smoking?"

●Manual for smoking restriction in medical institutions

●Leaflet for patients
"Keys to successful smoking cessation"

●Smoking cessation support procedures sheet
"Five steps leading to successful smoking cessation"

Fig. 2 Educational materials for the promotion of tobacco control in medical institutions

sionals under the Osaka Executive Committee of the Cancer Prevention Campaign, which aims to promote the control of tobacco use in medical facilities (Fig. 2). Smoking ban in a medical institution provides "a cleaner, more comfortable hospital environment" and is also expected to increase the motivation of patients and personnel who smoke to give up the habit. To give greater credence to medical programs aimed at treating nicotine dependence, smoking ban in medical institutions needs to be addressed. These educational materials are available for reading and downloading on the URL of the Osaka Cancer Prevention and Detection Center (http://www.gan-osaka.or.jp) (in Japanese only).

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