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CONTENTS

Basic Policies of the Japan Medical Association

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The following is a main part of the address of Dr. Eitaka Tsuboi, President of the Japan Medical Association, which was presented at the 109th Extraordinary General Assembly of the JMA House of Delegates that was held in Tokyo on October 12, 2003.

JMA's Basic Policy to Ensure Safety in Health Care

The medical accidents that have successively occurred in recent years have greatly shocked the nation; and it is a source of deep remorse that these accidents have led to the loss of public trust in our health care system.

Although some of these medical mistakes fall within the realm of highly advanced medical technology, these incidents are unforgivable irrespective of the causes, given the reality that there has been the loss of precious lives completely contrary to the promise of a more fulfilling life by the progress that has been made in medical technology.

We all know that the Hippocratic Oath forbids physicians from injuring patients through medical acts, and this is not limited to the field of advanced medical technology. Safety in health and medical care is the fundamental principle of medical ethics. Health and medical care personnel in charge of blood transfusions, medication, clinical tests, and a variety of other technical tasks must be stringently forced to recognize the ironclad rule that patients must not be injured or harmed through medical acts. The situation must be quickly remedied against the outbreak of such mistakes and the utmost effort must be made to appeal to health care personnel to take preventive measures against the reoccurrence of such accidents. Thus, in view of the situation, it is time for the JMA to actively propose specific measures to secure safe medical and health care. Emergency consultations have been held with the members of the self-improvement committee that was quickly created within JMA, the committee on health care safety, the committee on improving ethics, and various other relevant committees. Opinions on specific accident prevention measures will be solicited, a draft plan will be prepared, and following a decision by the executive board, it will be publicly announced to specialist medical societies, the government, politicians, and to the general public. JMA's readiness to take medical accident preventive measures and its action policy on this issue must be communicated; and it must take actions that will win back the public trust that has been lost.

In the past, the JMA expressed its concern when it pointed out the possibility that medical ethics might be undermined in the draft revision of the Declaration of Helsinki that was submitted to the Council meeting of the World Medical Association (WMA). JMA actively

expressed its opposition against putting a price on human life under any circumstances and to safeguard the dignity of citizens of economically weaker nations, notably the developing countries against its elimination in the name of globalization or economic efficiency.

High quality health care, highly safe health care is what humanity throughout the world yearns for at present. Thus, the JMA, which holds a position of leadership within international medical associations, must uphold steadfastly the principle and action that promote safe health care in Japan. JMA's proposals to secure safe medical and health care must be publicly announced as quickly as possible, and we must foster the public's sense of security.

Issues of Clinics with Beds, Retirement Age, etc.

Next, I would like to discuss issues related to the health care provision system.

The debate about abolishing Article 13 of the Medical Service Law that threatens the continued existence of clinics with beds, which has been a traditional aspect of Japan's health care culture, has been an ongoing debate for several decades. The viewpoints of the government administration and on-site clinics have constantly been at odds over the regulation restricting the hospitalization period at clinics to 48 hours despite the supplementary clause that allows this restriction to be extended at the discretion of the physician-in-charge. As a result, these clinics have not been efficiently operated. Thus, the JMA is currently in negotiations with the Health Policy Bureau of the Ministry of Health, Labour and Welfare (MHLW) over the complete abolishment of this Article. Although an in-depth study and concrete discussions have been conducted by members of JMA's committee in charge of reviewing this issue, it has been a difficult undertaking. But we are determined to continue the ongoing discussions and to achieve our goal. I believe that a potential solution can be reached if we study countermeasures that are fundamental structural reforms of the health care system of our country. This is the ardent wish of the JMA, and we would like to resolve the issue on abolishing Article 13 of the Medical Service Law that limits the hospitalization period of patients and other problems related to clinics with beds.

At the last House of Delegates meeting, I promised that the JMA would establish a committee to study its bylaws and provisions and comprehensively discuss the issues concerning clinics with beds, the integration of membership qualifications, and a retirement system for board members and delegates of 70 years and older. A committee was immediately created, and a committee report was submitted based on the subsequent discussions that have taken place. This report has been sent to each local medical association. As you are aware, their conclusion was that it was extremely difficult to implement an integrated membership qualification and retirement system. And I have just explained the situation about the issue regarding clinics with beds.

Based on an exchange of opinions with each regional block, we received your viewpoints about issuing medical certificates for various licenses and qualifications. We discussed the majority viewpoint with relevant MHLW personnel that in principle, doctors should refuse to issue a medical certificate if they cannot make an accurate diagnosis of the patient on his/her first visit. The MHLW has also indicated that they will set up a study team with the cooperation of the JMA at early date, and it will work towards compiling an intermediate position within this fiscal year. Therefore, we will have to wait a short while longer before a conclusion can be reached.

Nursing System

Next, I would like to discuss our nation's nursing care system.

As a nation with the world's most rapidly aging society and low birth rate, the remarkable progress that has been made in medical science has greatly improved and rapidly changed community health care both quantitatively and qualitatively. Under these circumstances, it is only natural that well-defined and specific improvements are being demanded of our nursing care system. Issues about what nursing and care for the elderly should be about or what improvements should be made in nursing to keep up with the progress that has been made in advanced medical technology are some of the many notable demands of the general public. I believe that the JMA must endeavor to build a nursing system that is in sync with the times, while simultaneously respecting the professionalism of nurses who are the partners in a community health care system.

Lately, the JMA has advocated the introduction of a team of nurses based on a three-tiered system of nurses, assistant nurses, and nurse aides in community health care as recommended by the ILO. JMA has especially pointed out the rising significance of the existing system of assistant nurses that is being re-acknowledged in the face of increasing care duties in an aging society. Moreover, in conjunction with the legislation of laws in recent years, caseworkers, nursing care workers, and personnel in a variety of health related occupations have arrived on the scene creating a multi-tiered nursing and care structure. This phenomenon is anticipated to diversify even more as social values change. Despite the shift into a new stage of development, the importance of a three-tiered nursing and care structure should not to be taken lightly. Physicians and nurses have been given the added task of jointly building a system based on an action plan with a mutual goal that will integrate the many personnel engaged in diverse occupations with different health and nursing concepts and achievements and to implement these myriad tasks effectively in the community.

The JMA, which has always advocated the importance of assistant nurses within a three-tiered structure, will continue to advocate their importance within a new social milieu; and it believes that creating such a nursing and care system is an urgent task. Specifically, a joint project team will be established by the JMA and the Japan Nursing Association aimed at completing a nursing system in Japan.

International Activities

Next, I would like to report on the international status of the JMA.

JMA's contribution to the WMA has increased yearly and recognition of its contribution continues to rise within the international community. This is because the JMA has actively stressed medical ethics; and its proposed statements that focused on improving medical safety were adopted. In addition, a working group was created to prepare a WMA declaration on water and health care that was proposed by the JMA.

Meanwhile, the JMA will host the CMAAO Congress from December 11 to 12, 2003 in Tokyo and the WMA Tokyo General Assembly on October 6, 2004 for a five-day period. The Board of Trustees has already approved the establishment of a preparations committee. Thus, JMA's record of achievements as an international medical association continues to grow. As an international medical association, I would like the JMA to contribute Japan's very outstanding expertise in health care to the prosperity of humanity throughout the world.

In addition, the progress made by the JMA medical assistance project in Nepal has been satisfactory. We are presently in the stage of transferring the management of the project's health activities to the Nepalese staff members. The success of the school education activity in Nepal can be attested to the fact that the literacy rate of the community has risen greatly and our efforts have been highly appraised by the Nepalese government.

The Takemi Program conducted jointly with

the Harvard School of Public Health in the United States continues to make progressive achievements thanks to the enthusiasm and dedication of all those involved in this program.

Revision of Medical Fees

I would like to extend my deep apologies and regrets as the head of the executive board for the truly grievous state of affairs for the more than anticipated damages that have been caused by the deficit revision of medical fees and the increased payments of patients. The negative effect on the operations of clinics and hospitals has been extensive.

Although some progress has been made to recover from these damages, the aftereffects have not disappeared and greater effort is needed.

The recovery of the remaining unadjusted segment in conjunction with the FY2004 revision of the medical fee schedule will be fundamentally debated through ongoing discussions with the Central Social Insurance Medical Council to ensure that the revision is consistent with the demands of the clinics and hospitals. Procuring financial resources is the most important factor in revising the medical fee schedule. We had begun negotiations with the Ministry of Finance, the MHLW, and relevant branches immediately after the previous revision had been announced, but we will begin lobbying activities with regard to the next revision of financial resources in tandem with our discussions with the Central Social Insurance Medical Council. Formidable effort will be made to convince the relevant ministries and divisions of our standpoint.

Difficulties in Health Reform

The Koizumi Cabinet's reform strategy, which promulgates "structural reforms without sanctuaries", has left the health care sector with numerous scars. The content of the Koizumi Cabinet's health care reforms are mainly characterized by the following two desires. Firstly, there are the health care reforms based on market principles that are aimed at making a profit by putting a price on human life. Specifically, the management of hospitals by private companies, the introduction of a combined payment system for diagnosis and treatment, and reforms that allow the Federation of Health Insurance Societies to select and sign direct contracts with health and medical institutions are some of the notable measures that are being promoted. The Cabinet's stance is that such deregulation measures are needed in order to improve the quality of Japan's health care. However, this stance may potentially violate the fundamental freedom of patients to select the medical institution of their choice as well as destroy the impartial system of health care that has been maintained thus far. Put in extreme terms, it is the same as saying, "we'll get rid of the pain of the rich, but poor people must endure". Such a system is completely unacceptable to the Japanese people.

Secondly, the Koizumi Cabinet would like to place the control of health care costs under the leadership of the government bureaucracy. They are trying to control the growth rate of elderly health care costs and the overall framework of controls for health costs through measures that require the least effort and exertion. Burgeoning health care costs are an acute problem, but policies by the Ministry of Finance that increase or decrease benefits according to their finances are not measures that have the welfare of the Japanese people in mind.

Presently, health care costs are estimated at 31 trillion yen. Market principle supporters believe that the greater this amount is the better, whereas the bureaucrats believe that the lesser these costs are the better. These composite contradicting poles of thought characterize health care reforms. Thus, health reforms in Japan have progressed without any consistency and only superficial reforms or changes that have been for the worse have been implemented, while radical structural reforms remain

unimplemented. Real structural reforms of the social security system are just beginning.

I announced my support for Mr. Koizumi in the last LDP presidential election; and there were many voices around me that opposed my support. I have been criticized and asked why I have supported Mr. Koizumi when the JMA has been thoroughly battered by his structural reforms. The health reforms that have been pursued by the Koizumi Cabinet are very inferior and I am aware of this fact. My reason for supporting him is that our social security system has reached its limits due to the haphazard measures that have been taken in the past. To seriously reform our system, I have acutely felt the need for the kind of drive displayed by Mr. Koizumi's reforms. We are in the stage where total social security reforms cannot be achieved without fundamental reform. It is important that there is a clear vision of our country's future before we put a scalpel to the existing social security system. When I scrutinized the other leaders in our political system, I did not see one political leader whom I thought would push furiously ahead with reforms. I believe that the increasing momentum to legislate national reforms provides a singularly unique opportunity to enact health care reforms.

Social Security System as Part of National Strategy

A national viewpoint and a perspective rooted in medical ethics are needed to implement fundamental health reforms. If the concepts of a new social security system are not based on these perspectives, the direction of these reforms will waver. As I stated at the previous House of Delegates meeting, the social security system must be expanded as part of the government's national strategy.

Employment must be secured and pensions must be properly paid to the elderly. These components of the social security system are issues that the government must address with just as much responsibility and earnestness as national defense. Politicians have traditionally viewed social security as a form of charity for the economically disadvantaged. What is even more frightening is that they believe that the national strategy is to utilize the financial resources set aside for the social security system for other policies. Social security as a means of relief for the economically disadvantaged is most certainly one aspect of the system, but it is not limited to this function alone. The goal is to create a social welfare system that benefits both the younger generation and the elderly.

What is needed in future is a social security system that provides for all stages of an individual's life cycle from birth, education, employment, pension, to the end-of-life care. The kind of social security system that we aim for is much broader in concept than UK's social security system, which is based on a concept of security "from cradle to grave".

However, living in an age where life values greatly change and in an advanced information society where we live under the illusion that we have reached the ultimate stage of development, a multifaceted information network that exceeds conventional methods must be established in order for each citizen to be convinced of a social security concept that is based on medical ethics according to his or her sense of values.

However, it is difficult to pursue this task successfully utilizing solely JMA's conventional latitude of professional knowledge; and a broader spectrum of expertise and technology from other sectors is needed. I acutely feel that the course that the JMA must adopt to cope with the strong public demand for diverse health care will require much energy and accumulated technology.

However, to realize this ideal and to build a society where social security is viewed as a part of the national strategy, the government administration and legislators must be persuaded of this fact based on public consensus. Thus, I believe that JMA's foremost responsibility is to strive untiringly toward this goal.

Extraordinary devotion and an exceptionally broad perspective will be required to successfully accomplish this important and difficult task. Superior leadership of the president and the resilient unity of all JMA members are vital factors. Thus, standing at this juncture today and with an awareness of my limitations, I have decided not to run for the office of president in the next JMA presidential election.

I have worked as an executive member of the JMA for the past 15 years since I was elected to the Executive Board of Trustees in October 1988. During this 15-year tenure, I have served in the office of president for four terms or eight years since 1996. I am confident that the JMA will make a giant leap forward with the understanding of the Japanese public to help build our nation into the foremost health care nation in the world. With these words, I would like to conclude the president's policy speech for the 109th JMA Extraordinary House of Delegates meeting. Thank you very much.

Basis and Clinical Applications of Interferon

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Abstract: Interferon (IFN) is an antiviral substance that was discovered about 50 years ago. The advance in the basic research of IFN has revealed the action mechanism of its antiviral effect at a molecular level and provided wide clinical applications. It is roughly divided into 3 types: IFN-α, IFN-β, and IFN-γ. IFN-α is related to IFN-β, but IFN-γ is completely different. Any type of IFN is a (glyco) protein with a molecular weight of about 20,000 kDa. IFN is known to have various biological activities including antiviral effects. Major biological activities include cell growth inhibition and immune regulation. Anti-tumor effect of IFN develops by integration of the various biological activities. IFN is considered to exert its antiviral effect by not only directly inhibiting viral proliferation, but also stimulating cytotoxic T cells, natural killer cells, and macrophages.

Key words: Interferon; Inhibition of viral proliferation; Immunomodulating effect; NK cell; Helper T cell

Introduction

Interferon was first discovered by Nagano and Kojima[1] in Japan as a virus inhibiting factor in 1954. It was also discovered by Isaacs and Lindenmann[2] in 1957 as a substance responsible for virus interference. About a half century has passed since its discovery. It has been clinically applied to treat various diseases for more than 20 years. This paper outlines interferon and explains the results of the basic research toward its clinical application.

Types and Properties

Interferon (IFN) is generally classified into 3 types (Table 1). First, IFN-α is produced when leukocytes are infected with a virus. It is also called leukocyte interferon. Second, IFN-β is produced when fibroblasts are infected with a virus or treated with synthetic double-stranded RNA (polyinosinic acid/polycytidylic acid complex; poly I:C). It is also called fibroblast interferon. Third, IFN-γ is produced when lymphocytes are stimulated with a mitogen or sensitized lymphocytes are bound to an antigen. It is also called immune interferon.

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Table 1 Types and Properties of Human (Hu) IFN

	Type I			Type II
	HuIFN-α		HuIFN-β	HuIFN-γ
	Normal HuIFN-β	HuIFN-ω		
Molecular weight	About 20,000	About 20,000	About 20,000	About 20,000 (monomer) About 40,000 (dimer)
No. of amino acids	165–166	172	166	146
No. of genes	23 or higher (including 4 pseudogenes)	About 7 (including 6 pseudogenes)	1	1
Subtype	14 or higher	1	1	1
Intron	0	0	0	3
Gene location	9p21	9p21	9p21	12q24.1
Presence/absence of sugar chain	No	Yes	Yes	Yes
Antigenic type	α	α	β	γ
Main producer cell	Leukocyte	Trophoblast	Fibroblast	Th1<NK
Receptor	Type I (common to α, β and ω)	Type I (common to α, β and ω)	Type I (common to α, β and ω)	Type II (specific to γ)
Receptor gene location	21q22.1	21q22.1	21q22.1	6q16-q12
Species specificity	Weak	Weak	Weak	Strong

IFN-α is similar to IFN-β because both have 166 amino acids (some types of IFN-α have 165 amino acids) and because there is about 50% homology for their amino acid sequences, or the nucleotide sequences that code them. Furthermore, since the genes for IFN-α are located at the same chromosome as that for IFN-β (9p-21 for humans), IFN-α is genetically related to IFN-β. It has been revealed that IFN-α has 14 or more subtypes, and that there are 23 or more genes for IFN-α including pseudogenes. In contrast, IFN-β has one gene and one subtype.

IFN-ω, a subtype of IFN-α, has 172 amino acids. The genes for IFN-ω are also located at the same chromosome and there is 60% or higher homology for amino acid and nucleotide sequences.[3)]

Another type of IFN is produced from placental trophoblasts and called trophoblast IFN. This type of IFN is also called IFN-τ. It is considered to be closely related to the recognition of pregnancy by the parent body.[4)]

One recent development is a form of consensus IFN-α that has a structure common to the subtypes of IFN-α. The consensus IFN-α is considered to provide higher efficacy than normal IFN-α, with fewer adverse effects.

IFN-γ usually exists as a dimer and has 146 amino acids, 20 fewer amino acid as compared with the 166 amino acids of IFN-α or IFN-β. It has one gene located at the chromosome of 12q24.1 for humans. These facts indicate that IFN-γ is completely different from IFN-α or IFN-β.

Table 2 Various Biological Activities of IFN

1. Anti-tumor effect
2. Inhibitory effect on cell growth
3. Effects on lymphocytes
   a) Stimulation and inhibition of antibody production (B cell)
   b) Inhibition of delayed-type hypersensitivity (T cell)
   c) Inhibition of transplantation immune response (T cell)
   d) Inhibition of blastogenesis and DNA synthesis (T cell)
   e) Potentiation of killer T cells (T cell)
   f) Potentiation of natural killer activity (NK cell)
   g) Potentiation of ADCC activity
4. Effects on macrophages
   a) Potentiation of phagocytosis
   b) Potentiation of adherence to tumor cells
   c) Inhibition of intracellular bacterial proliferation
   d) MIF activity
   e) Chemotaxis
5. Other effects on cells
   a) Chemotaxis for neutrophils
   b) Potentiation of NBT reduction in neutrophils
   c) Increased histamine release in basophils
   d) Promotion of differentiation of erythroblasts
   e) Induction of differentiation of neuroblastoma cells
   f) Potentiation of expression of MHC Class I and II antigens

Biological Activity

Many of the various biological activities of IFN are known and understood (Table 2). Naturally enough, since it was first discovered as an antiviral agent, we know that it engages in antiviral activity (inhibits viral proliferation). Other known activities include inhibition of cell growth and effects on immunological activity.

In general, IFN stimulates macrophage and natural killer (NK) activities and plays important roles in host defense. IFN, particularly IFN-γ, plays a key part in regulating the biological immune response, as described below. It is also considered that IFN exerts its effects on viral infection and malignant tumors, as described in the following sections, by combining all of its diverse biological activities.

1. Antiviral activity

The mechanism of antiviral activity of IFN (inhibition of viral proliferation) has been generally revealed (Fig. 1). The binding of the IFN molecule to its receptor activates two enzymatic systems. One is the 2-5A synthetase system (2-5A oligosynthetase). When the enzyme is activated, 2-5A is synthesized in the presence of ATP and double-stranded RNA. 2-5A activates endo-RNase (endonuclease) to degrade viral mRNA, thereby inhibiting viral protein synthesis.

The other enzymatic system is protein kinase (PKR), which is also activated in the presence of double-stranded RNA. When activated, it phosphorylates the initiation factor-2α (eIF-2α) required for starting the synthesis of peptide chains on ribosomes, thereby inactivating eIF-2α. This prevents the virus from commencing protein synthesis on the ribosome, and results in the inhibition of viral proliferation.

In addition to the two enzymatic systems responsible for the inhibition of viral proliferation, other known mechanisms include the inhibition of transcription into viral mRNA and viral inhibition at the viral particle budding phase. It is considered that appropriate action

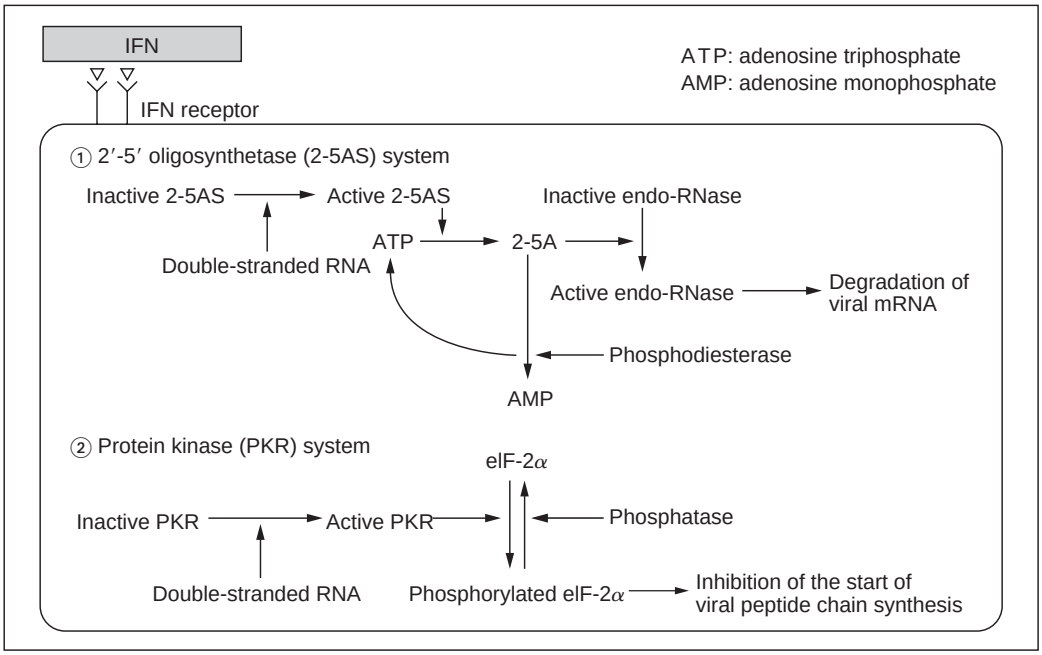

Fig. 1 Mechanism of antiviral effect of IFN

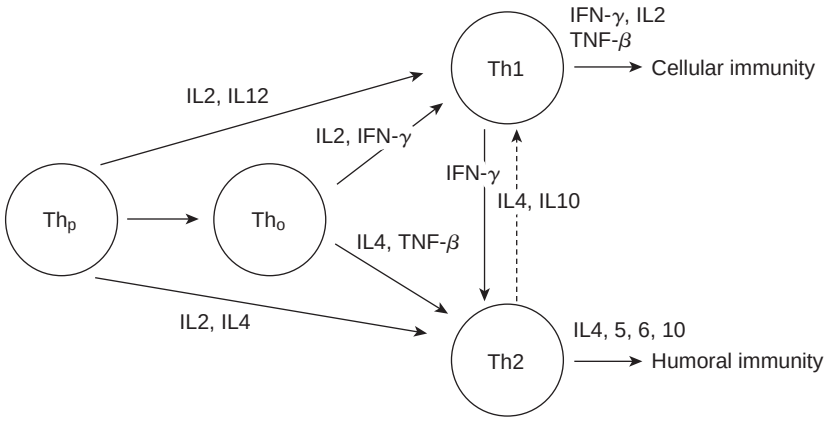

Fig. 2 Th1 and Th2 cytokine

mechanisms of IFN may function depending on viral type.

2. Effects on the immune system

IFN has been known to have many effects on the immune system. It is considered to generally inhibit antibody production and delayed-type (Type IV) hypersensitivity. However, it stimulates cytotoxic T cells (killer T cells), NK cells, killer cells responsible for antibody-dependent cell-mediated cytotoxicity (ADCC), macrophages, and neutrophils.

IFN-γ has a regulatory effect on the immune system: that is, IFN-γ is produced from type 1 helper T (Th1) cells. It is also known to stimulate the growth of Th1 cells. Since Th1 cells are involved in cellular immunity, IFN-γ is considered to increase cellular immunity. In con-

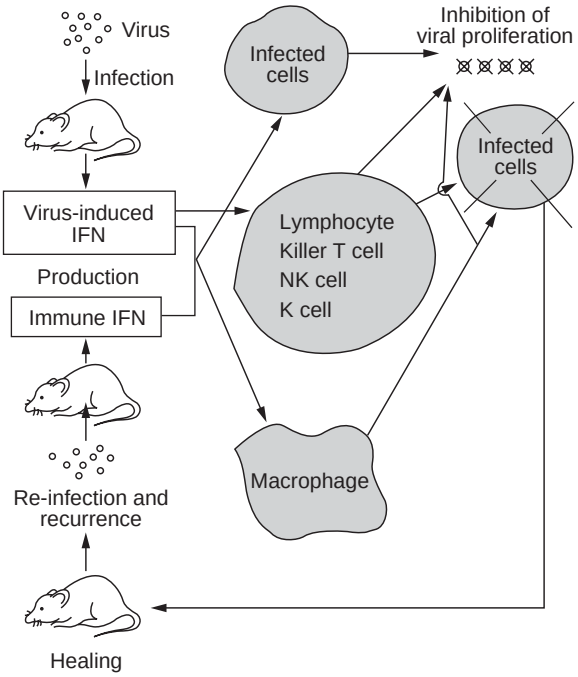

Fig. 3 Antiviral effect of IFN

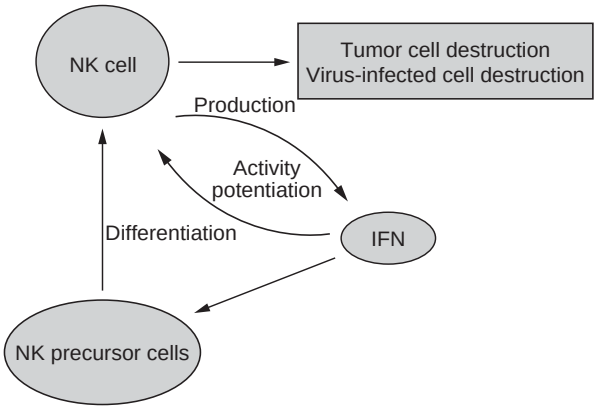

Fig. 4 IFN-NK system

trast, since IFN-γ suppresses the activity of Th2 cells, it is considered to suppress humoral immunity (Fig. 2).

Effects on Viral Infections

For the action mechanisms of IFN on viral infections, IFN directly provides antiviral effects and indirectly inhibits viral infections through the immune system (Fig. 3). IFN enhances the activities of macrophages, NK, and ADCC to inhibit viral proliferation in infected cells and destroy infected cells.

It is considered that the same mechanisms work for tumors. IFN directly inhibits the proliferation of tumor cells, and generally has a stronger growth inhibitory effect on tumor cells than on normal cells. IFN is also known to induce apoptosis in some cells. Thus, IFN not only directly inhibits the proliferation of tumor cells or destroys them, but also indirectly inhibits them by stimulating the immune system. As described above, IFN is known to enhance the activity of killer T cells, NK cells, and ADCC, and to stimulate macrophages and neutrophils to destroy tumor cells.

IFN is known to form a cycle with NK cells. That is, IFN increases NK activity, activated NK cells produce IFN, and IFN acts on NK precursor cells to induce the differentiation of NK cells, thereby increasing NK cells. This system formed by IFN and NK cells is called IFN-NK system (Fig. 4). The IFN-NK system is deeply involved in host defense against viral infection and against tumors. It is well known that the IFN-NK system strongly inhibits tumor metastasis.

Conclusions

IFN engages in various biological activities including antiviral action. It combines all its activities to provide protection against viral infections and tumors. It is important to clinically apply IFN by managing both the direct and indirect effects of IFN.

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Interferon Therapy for Leukemia

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Abstract: Most patients with chronic myeloid leukemia (CML) have leucocytosis, anemia, and splenomegaly. The natural history of CML is progression from a benign chronic phase to a rapidly fatal blast crisis within three to four years. The diagnosis of CML is usually based on detection of the Philadelphia (Ph) chromosome. Ph chromosome abnormality is t(9;22). The molecular consequence of the t(9;22) translocation is the creation of a fusion protein BCR/ABL which is a constitutively active cytoplasmic tyrosine kinase. Interferon (IFN) α is capable of inducing hematological control in 80–90% of patients and a major cytogenetic response in 30–50%. In practice, 3–6 million units of subcutaneous IFN is used. The most common side effects are fever, fatigue, and appetite loss. IFN should be used cautiously in patients with a history of serious depression because it may exacerbate this problem. The addition of low-dose cytarabine to IFN increased the cytogenetic response rate. Hairy-cell leukemia (HCL) is an uncommon B-cell chronic lymphoproliferative disorder. IFN, splenectomy, and purine analogues are the treatment options for HCL.

Key words: Chronic myeloid leukemia; Interferon; Cytogenetic response; Hairy cell leukemia

Introduction

Interferon (IFN) has various biological activities including the inhibition of viral proliferation. The induction of cytotoxic T cells is considered one of the action mechanisms of the antitumor effect of IFN. Tumors of hematopoietic organs for which IFN is effective include chronic myeloid leukemia (CML), hairy cell leukemia (HCL), multiple myeloma, and malignant lymphoma.

Chronic Myeloid Leukemia

CML increases leukocytes and causes splenomegaly and anemia. The chronic phase is characterized by increased leucocytes proceeding to the blast crisis in 3 to 4 years unless optimal treatment is given. The blast crisis of the disease shows a pathology similar to acute leukemia. Since it does not respond to chemotherapy, it often leads to death within 1 year. Therefore, the target of CML treatment is to

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Table 1 Decision Criteria for IFN Effect for Chromic Myeloid Leukemia

• Hematological response	• Cytogenetic effect
Complete hematological response (CHR)	Ph^1 positive rate
Normal leukocyte count	CCR 0%
Elimination of juvenile granulocytes	PCR＜35%
Platelet count＜450,000	MCR 35 to 94%
Elimination of clinical symptoms, such as splenomegaly	NR 95 to 100%
Partial hematological response (PHR)	
Leukocyte count of 50% or lower of pretreatment level, and of fewer than 20,000	
Normal leukocyte count, but with residual immature granulocytes	
Persistent splenomegaly	

prolong the chronic phase as much as possible by preventing blast crisis.

The blood cells of CML show a reciprocal translocation in which a part of the 9th chromosome is replaced with a part of the 22nd chromosome, which is designated the Philadelphia (Ph) chromosome. This chromosome produces an abnormal gene called BCR/ABL fusion gene, which has been considered to stimulate tyrosine kinase activity and cell growth, leading to leukemia.

Thus, the identity of CML lies in the increase in the cells with the Ph chromosome, and the target of CML treatment is to reduce them. Busulfan and hydroxycarbamide have been used to treat CML and reduce leucocytes, but they have almost no effect on reducing cells with Ph chromosome. The following three therapeutic methods are available to reduce these cells: (1) hematopoietic stem cell transplantation, (2) interferon (IFN) therapy, and (3) therapy with imatinib mesilate, which has recently become available in Japan.

Interferon Therapy for Chronic Myeloid Leukemia

IFN normalizes leucocytosis and splenomegaly in most patients with CML. This is called a hematological response and achieved in 80 to 90% of patients with IFN. The effect of IFN in reducing Ph chromosome-positive cells is called a cytogenetic response. Table 1 shows the criteria for hematological and cytogenetic responses. The disappearance of Ph chromosome-positive cells from the bone marrow on examination six months to one year after the start of IFN therapy is called complete cytogenetic response (CCR) and the reduction of the cells to less than 35% of the pre-treatment level is called partial cytogenetic response (PCR). The combination of CCR and PCR is called major cytogenetic response (MCR). It is generally considered that 30 to 50% of chronic phase patients treated with IFN achieve MCR. Figure 1 shows the relationship between the cytogenetic effects of IFN therapy and the survival period of CML patients at the M.D. Anderson Cancer Center.[1)] It shows that 38 patients achieved MCR, and only three of them died in 60 months, indicating a significantly longer survival period for these patients, as compared with those who could not achieve MCR.

The Euro score is an index to predict the response to IFN in CML patients.[2)] It is based on the analytical results of IFN therapy in a total of 1,573 CML patients in 12 medical institutions worldwide. Table 2 outlines this score. The score is calculated using the following parameters: age, spleen size, and count of blast cells, basophils, eosinophils, and platelets. Based

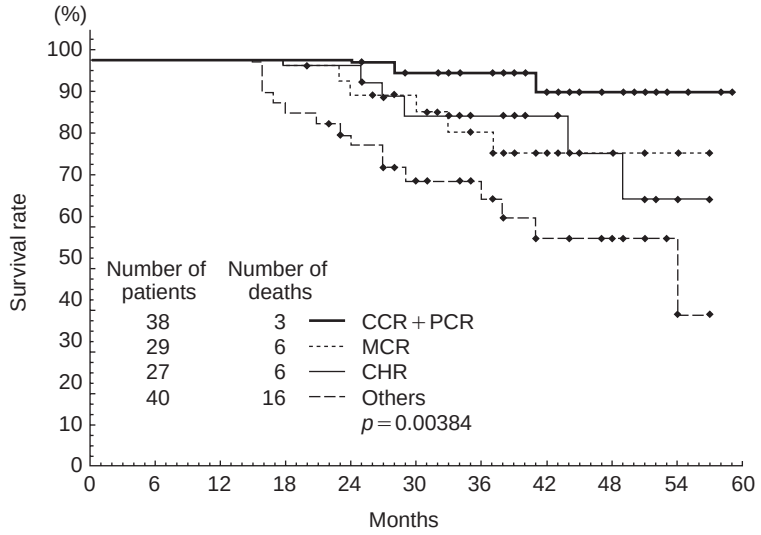

Fig. 1 IFN therapy for CML: survival by cytogenetic effect
(Kantarjian, H.M. *et al.*: *J Clin Oncol* 1999; 17(1): 284–292)

Table 2 Prognostic Score of IFN Therapy for Chronic Myeloid Leukemia (Euro score)

• Prognostic score
= {0.6666 × age* + 0.0420 × spleen size (cm)
+ 0.0584 × blast (%) + 0.0413 × eosinophil (%) + 0.2039 × basophil**
+ 1.0956 × platelet count***} × 1,000
*: age: less than 50 years = 0, 50 years or older = 1
**: basophil: less than 3% of peripheral blood basophil = 0, 3% or higher = 1
***: Platelet count: less than 1.5 million = 0, 1.5 million or higher = 1

	Prognostic score	5-year survival
Low risk	780 or lower	76%
Intermediate risk	780 to 1,480	55%
High risk	1,481 or higher	25%

on this score, CML patients are classified into three groups of low, intermediate, and high risk: the five-year survival rate of these groups is 76%, 55%, and 25%, respectively. This indicates that long-term survival cannot be expected from the IFN therapy in the high-risk group. Another index to classify the risk of CML is the Sokal score obtained by analyzing survival results by busulfan therapy before IFN was introduced. The Sokal score is the same as the Euro score except that it does not include the eosinophilic and basophilic counts. The Sokal score has also demonstrated that the low-risk group would achieve prolonged survival with IFN therapy.

Practice of Interferon Therapy for Chronic Myeloid Leukemia Patients

Usually, patients with chronic phase CML are treated with self-injection of 3 to 6 million units of IFN. The adverse effects of therapy include fever, chills, headache, myalgia, general malaise, anorexia, nausea, vomiting, and diar-

rhea. These adverse effects are often resolved by continuing the IFN therapy and can often be overcome with drugs such as antipyretics.

It is considered important to continuously administer the maximed tolerable dose of IFN to maximize the therapeutic effect of IFN therapy for CML. Higher cytogenetic effects can be expected from therapy if one avoids reducing doses or lengthening the intervals between administration (which one might be tempted to do in the presence adverse effects such as fever, malaise, and anorexia). It is therefore essential to inform the patients fully about CML and make them fully understand the significance of IFN therapy. We have used the survival curve in Figure 1 to help the patients understand the fact that the cytogenetic effect produced by IFN prolongs survival.

Clinically important adverse effects of IFN include psychological and nervous symptoms including depression. Particular attention should be paid to patients who have depressive tendencies before starting IFN therapy, because IFN may cause severe depression leading to a suicide attempt.

Self-injection of IFN reduces leucocytes to the normal level, eliminates splenomegaly and other clinical symptoms, and improves hematological status by bringing the platelet count to normal. This complete hematological response is achieved in 80 to 90% of chronic phase CML patients treated with IFN. It is considered that failure to achieve such a response indicates difficulty in achieving a cytogenetic response. Therefore, IFN therapy should be stopped if no complete hematological response is achieved 6 and 12 months after IFN therapy has started. Our experience shows that no cytogenetic response can be expected unless the leucocyte count falls below 5,000/μl (Table 3). However, reducing the leucocyte count to less than 5,000/μl may reduce platelets or hemoglobin as well, preventing patients from continuing IFN therapy. IFN therapy should be continued for at least one year. If bone marrow examination one year after therapy was started shows a reduction in Ph chromosome-positive cells, MCR may be achieved by continuing the therapy even if MCR has not been achieved at the time of examination.

Table 3 Relationship between Leukocyte Count and Cytogenetic Effect

Leukocyte	CCR + PCR	NR
5,000>	12/24 (50%)	5/24 (20%)
5,000≤	0	7/24 (30%)

$p = 0.046$

(Derived from results in Department of Hematology, Tokyo Women's Medical University)

Combination Therapy with Interferon and Other Agents for Chronic Myeloid Leukemia

Combination therapy of IFN with cytarabine has been reported to increase the cytogenetic response of IFN by about 10%.[1] However, it is difficult to perform combination treatment in Japan because self-injected cytarabine is not available. An oral preparation of cytarabine, cytarabine ocfosfate, is available in Japan, but the combination of IFN and this preparation has been reported in a few cases of CML, and the combined effect remains unclear.

A study from the M.D. Anderson Cancer Center has reported combination therapy with IFN and GM-CSF for CML.[4]

Imatinib mesylate, a tyrosine kinase inhibitor active for the BCR/ABL fusion gene, has been reported to provide higher efficacy for CML than IFN.[5] Although it provides higher efficacy than IFN during the early stage, it is feared that it may induce early resistance because of its simple structure. To overcome the resistance, a trial on the combination of IFN and imatinib mesylate is now underway in the U.S. It should be noted that long-acting PEG interferon, which is approved only for type C hepatitis in Japan, is being used in that trial.

Interferon Therapy for Hairy Cell Leukemia

HCL is characterized by the development of cells with many hairy cytoplasmic projections. Since it becomes chronic, it is classified as a chronic leukemia. Typical hairy cells in Western countries are positive for tartrate-resistant acid phosphatase staining. There is a subtype called "Japanese type HCL", and its hairy cells show only weak tartrate-resistant acid phosphatase staining. Both types of HCL often cause splenomegaly.

HCL is treated with IFN therapy, splenectomy, and purine analogues. Recently, the efficacy of anti-CD20 antibody, rituximab, has been reported. The standard therapy for HCL should be started with splenectomy and, if the disease progresses, treatment with IFN or purine analogues should be considered.

The IFN therapy for HCL is based on the administration of 3 to 5 million units/day of IFN-α consecutively 3 times a week. The response rate of this therapy ranges from 50 to 90%.[6] Treatment with IFN improves blood cell abnormalities and reduces splenomegaly. Smaller doses of 0.2 to 0.6 million units of IFN will reduce the adverse effects, but will also reduce the efficacy rate. It is generally considered that the efficacy of IFN therapy for Japanese type HCL is lower than that for the European/American type.

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Practice of Interferon Therapy
—Brain tumor—

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Abstract: This paper outlines the current clinical application of interferon-β for treating brain tumor. Since approved as a therapeutic drug for brain tumor, IFN-β has been reported to be effective when it was used alone, in combination with chemo-radiation therapy (IAR therapy), and as a maintenance therapy. Recently, the regimens with IFN-β have been improved to obtain a higher efficacy rate. For example, liposome is used as a drug delivery system (DDS) to administer IFN-β protein or genes. Although much remains to be examined about administration methods for DDS, it is expected that new developments in the field of gene therapy will improve the therapeutic results of antitumor therapies by cytokines including interferon.

Key words: Brain tumor; Interferon-β; IAR therapy; Gene therapy

Introduction

Interferon (IFN) was discovered in the 1950's during research on viral interference, and its antitumor and other effects were reported from the 1960's. During the 1970's, attention was paid to IFN as an anti-cancer drug because its antitumor effect was reported in clinical studies. Now, it is clinically used to treat Type C hepatitis, multiple sclerosis, and various tumors including renal tumor, malignant melanoma, and brain tumor.

IFN is classified by its properties into 3 types: IFN-α, IFN-β, and IFN-γ. IFN-α and IFN-β code common gene loci and have common cellular surface receptors, while IFN-γ has different dynamics. Therefore, the former and latter are called Types I and II IFN, respectively. In the clinical application of IFN for brain tumor, IFN-α is mainly used in Western countries, while IFN-β was approved by the Ministry of Health, Labor, and Welfare and has been clinically used in Japan.

This paper describes the history of the clinical application of different types of IFN for brain tumor, current issues, and prospects for

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new therapeutic techniques.

Interferon Single Therapy

In studies of the antitumor effect of IFN-α and IFN-β using brain tumor cells, Lundblad[1] and Wakabayashi[2] reported a direct inhibitory effect on brain tumor, and Otsuka *et al.*[3] reported an indirect inhibitory effect through immunocompetent cells. Nakagawa and Ueda reported the clinical effect of IFN-α on malignant brain tumor: they achieved partial response in patients with glioblastoma and medulloblastoma by the systemic and local administration, respectively, of IFN-α. Subsequent phase II studies on the use of recombinant IFN-α for malignant glioma showed a response rate of 10.3 to 20%.

Nagai *et al.*, who performed the systemic and local administration of IFN-β, reported an overall response rate of 22.2% in 54 evaluable patients, and the response rates of 16.7% and 42.9% in patients with glioblastoma and medulloblastoma, respectively.[4] In 10 patients with malignant glioma, Yoshida *et al.* systemically administered 3×10^5 to 3×10^6 units of IFN-β for 16 to 50 days continuously via an intravenous route or locally administered 5×10^4 to 3×10^6 units into the tumors for 7 to 73 days continuously via an Ommaya reservoir implanted when a tumor was removed. The result showed the size of the tumor was reduced by 50% or higher in 2 of 7 systemically treated patients and 1 of 3 locally treated patients.

However, it was reported that, in any case, the antitumor effect after the administration period lasted for only a short period, and that the administration of IFN alone would not eventually prolong survival, although it might provide remission during the administration period. Therefore, investigators started to attempt various regimens with IFN.

Interferon Combination Therapy

To improve the therapeutic results of the interferon single therapies for brain tumor, combinations with other therapies or drugs were attempted. So far, the following combinations have been examined.

1. Combination with radiotherapy

For the combination with radiotherapy, which has been the most effective adjuvant therapy for malignant brain tumor, Miyoshi *et al.*[5] and Korosue *et al.*[6] performed basic research with IFN-α and IFN-β, respectively. The following hypotheses were obtained: partially synchronized radiotherapy with IFN in relation to the DNA synthesis inhibiting effect of IFN might be effective; IFN might play a role by sensitizing patients to radiation; and there might be an interaction between sublethal damage by radiation and the direct antitumor effect of IFN.

Regarding clinical applications, Mahaley *et al.* reported that the combination of radiotherapy and IFN significantly prolonged the median survival time in patients with malignant glioma, and that the combination provided better results than the combination of radiotherapy and BCNU (carmustine), which was previously the standard therapy for brain tumor patients in the institution.[7]

2. Combination with chemotherapy

Various combinations of IFN and anticancer agents have been examined. The Mayo Clinic reported that the combination of BCNU and IFN-α caused a significantly higher synergistic effect than that with other drugs in 35 patients with recurrent glioma: the combination achieved an efficacy rate of 29% and a period of 10.1 months, and blocked the progression of the disease for 6 months or longer in 37% of the patients. Nitrosourea anticancer drugs, such as ACNU (nimustine hydrochloride) and MCNU (ranimustine), are available in Japan, but single therapy with any of the drugs has been effective for only 30 to 50% of patients with brain tumor.

Examination of the combination of IFN-β and ACNU with 13 human glioma cell lines showed the combination 5 mg of ACNU and

1×10^3 IU of IFN-β provided a tumor proliferation inhibiting effect of at least 2 log cell kill, and that the effect was obtained in 9 cell lines, as compared with 2 and 1 cell line by the single therapy with ACNU and IFN, respectively. Further, the effect was higher than that of at least 2 log cell kill observed in 7 cell lines treated with 10 mg of ACNU alone.[8] When ACNU is clinically applied at a usual dose of 2 to 3 mg/kg body weight, the concentration obtained in brain tumors is approximately 1 to 5 mg. It is practically impossible to increase the dose because of possible adverse effects, such as bone marrow suppression. Therefore, the results indicating the potentiation of the antitumor effect more than the addition of the effect of each anticancer drug and IFN at a usual dose suggest the effectiveness of the combination therapy.

3. Combination with radio-chemotherapy

Since the combination of IFN-β and ACNU showed high antitumor activity in a basic experimental study with a human glioma cell line, a clinical study was started in Japan by combining the IFN-β and ACNU combination therapy with radiotherapy (IFN-β-ACNU-Radiation [IAR] therapy) as an adjuvant therapy for malignant glioma. Yoshida *et al.* reported that the prognosis as determined by the mean survival period was significantly improved with IAR therapy (25.3 months) as compared with radiation alone (15.2 months) and radiation + ACNU (19.7 months), and that the initial response rate by IAR therapy was higher than that by radiation + ACNU (60.5% vs. 35.7%). Further, Yoshida *et al.* also confirmed the efficacy of IAR therapy in 175 malignant glioma patients followed for a long time.[9] Hatano *et al.* reported that increasing the administration frequency of IFN-β to twice daily increased its antitumor effect.[10] A U.S. study on the combination of IFN-α, BCNU, and radiation for malignant brain tumor reported a median survival time of 12.7 months and a mean survival time of 16.1 months for Grade IV astro-

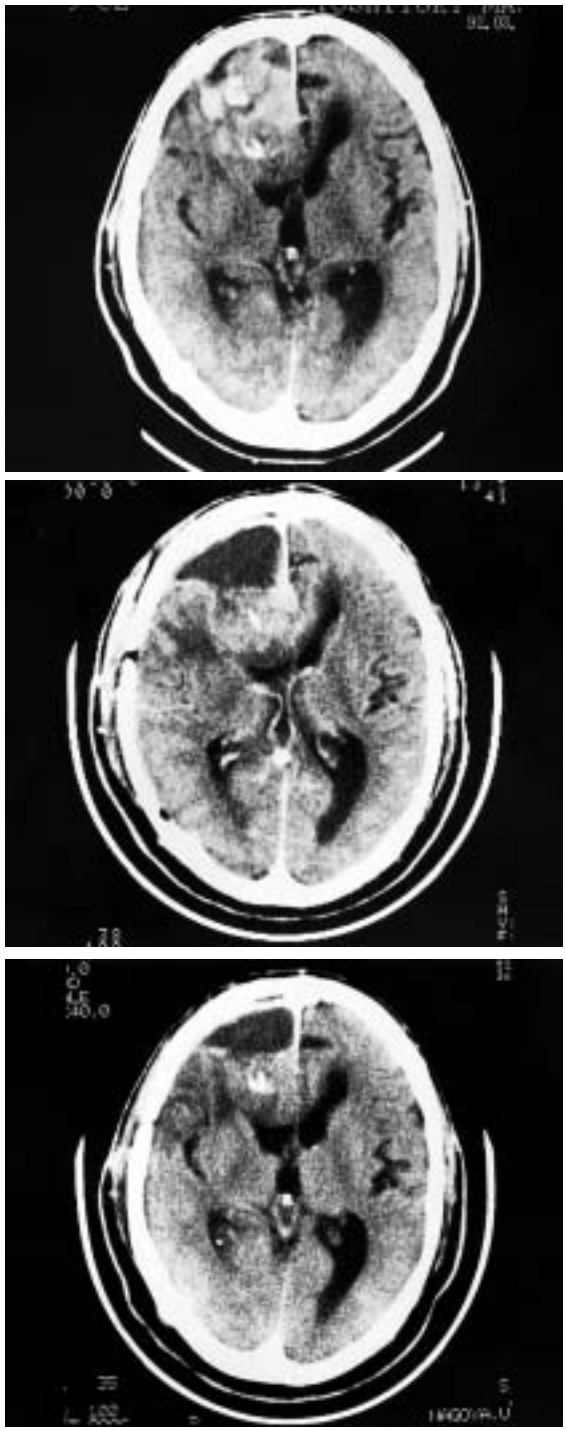

Fig. 1 54-year-old male patient: An enhanced lesion on CT scan indicating a tumor was observed in the right frontal lobe (a). It was diagnosed as glioblastoma. Since the postoperative image showed a residual tumor (b), IMR therapy was performed. A marked reduction of the tumor was observed at the end of the initial induction therapy (c). This patient received 3-month maintenance therapy, with no tumor recurrence for the subsequent 2 years.

cytoma, and 46.3 and 61.3 months for Grade III astrocytoma.

These results indicate that the inter-disciplinary combination of IFN-β, nitrosourea drug, and radiotherapy should be the first-line initial adjuvant therapy for inducing remission after an operation for malignant brain tumor (Figs. 1-a, b, and c). However, since recurrence was observed in most of the cases who responded to the combination, it is necessary to establish an appropriate maintenance therapy at an early stage after the induction of initial remission.[11]

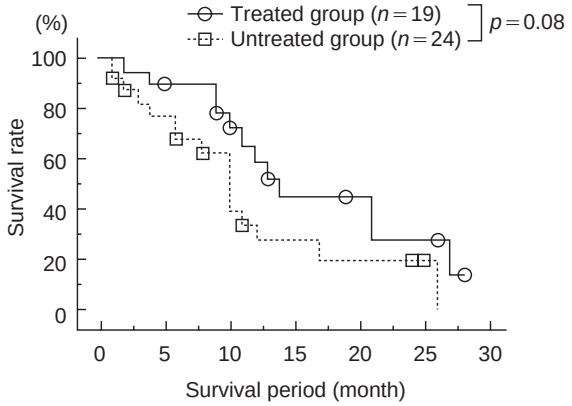

Fig. 2 Comparison between groups treated with and without IMR maintenance therapy

Interferon Maintenance Therapy

Although up to 60% of patients with malignant brain tumor could achieve remission by initial induction therapy, most of them experienced recurrence. For example, the remission and mean survival periods of patients with glioblastoma were reported to be as short as 11.2 and 13.9 months, respectively. Therefore, various maintenance therapies following initial induction therapy are being examined.

Wakabayashi *et al.* performed IFN-β-MCNU-Radiation (IMR) therapy as an initial induction therapy in patients who developed malignant glioma for the first time, and compared the remission period between those treated with a maintenance therapy consisting of 1×10^6 units of IFN-β every 2 weeks and 80 mg/m^2 of MCNU every 6 weeks for at least 3 months after the end of the induction therapy and those not treated with it. The patients registered into the initial induction therapy were randomly divided into 2 groups with and without the maintenance therapy, and they were compared for time to tumor progression (TTP) and total survival period. The results showed a significantly prolonged survival period in the maintenance therapy group (Fig. 2). Particularly, the patients who achieved complete remission by the initial induction therapy appeared to achieve a significantly prolonged remission period by receiving the maintenance therapy. It was also suggested that a certain therapeutic effect could be expected from the maintenance therapy in patients who developed the disease for the first time at 47 years or younger, or who achieved a partial response or a better response with the initial induction therapy. These results suggest that both initial induction and maintenance therapies may be important for the treatment of malignant glioma.[12]

New Developments in Interferon Therapy

1. Drug delivery system (DDS)-combined interferon (liposome)

Although IFN-β has been clinically applied for treating brain tumor, the clinical efficacy of IFN-β alone is less than expected when it was introduced in an uncombined form. It seems necessary to combine it with other therapies or drugs to fully realize its potential. In fact, IFN-β shows a marked antitumor effect at as low as 100 units *in vitro*, while it has been reported to produce tumor reduction by 50% or higher only in 15% of clinical cases, even at 10 million units. This difference in the efficacy of IFN may be explained by the pharmacokinetics of IFN, its stability in blood or tissue, or the blood brain barrier.

In an effort to overcome the problem of the

low *in vivo* effect of IFN, liposome has been examined as a drug delivery system (DDS). Epstein *et al.* examined the embedding of IFN in liposome and successfully changed the biological activities and pharmacokinetics of IFN. Kato *et al.* added sulfatide to liposome as a component to deliver IFN through the blood brain barrier into the cerebral parenchyma, and compared the stability, pharmacokinetics, intraorgan distribution, and antitumor effect between the embedded and free IFN. The result showed the blood titer of the free IFN became undetectable as early as 2 hours after intravenous administration, while the liposome-embedded IFN was detected at as high as 10^3IU/m*l* or higher even 8 hours after administration. Further, an IFN titer of 100IU/g tissue or higher was confirmed in the brain and subcutaneously implanted brain tumor tissue where no IFN was detected after the intravenous administration of the free IFN. It is expected that the clinical application of DDS will progress to increase the effectiveness of IFN for brain tumor.[13)]

2. Interferon gene therapy

Larsson *et al.* reported that endogenous IFN-β was produced from glioma cells using a super-induction technique. This glioma-derived endogenous IFN-β has an antitumor effect on human glioma cells. We have been developing IFN gene therapy in which human IFN-β genes are embedded in the liposome with an affinity for glioma cells to selectively introduce the liposome into glioma cells and locally generate a large amount of endogenous IFN-β, thereby causing an antitumor effect on glioma. Since this technique ensures the secretion and maintenance of a much higher local concentration of IFN than administration from outside, the so-called paracrine effect can be expected. Further, the technique has been reported to cause phenomena that have not been observed with exogenous IFN, such as the induction of apoptosis of transgenic glioma cells. Finally, we expect an association with the immune system to indirectly enhance the antitumor effect.[14)]

A clinical study on the gene therapy for brain tumor (malignant glioma) using this positively-charged liposome embedded-human IFN-β gene (local injection of the IFN-β gene-embedding liposome into brain tumor) was started on April 3, 2000 at the Nagoya University Hospital. So far, 5 patients have been registered and examined for the safety and efficacy of the therapy. The results of the study will be reported soon.

Conclusions

This paper outlines the current clinical application of interferon to brain tumor. There remains much to be examined about the use of IFN, such as appropriate administration regimens and the importance of maintenance therapy. However, together with the new developments in IFN therapy including the use of DDS and gene therapy, it is expected that the therapeutic results of antitumor therapies with cytokines including IFN will be improved.

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Interferon Therapy in the Field of Dermatology

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Abstract: Interferon therapies for dermatological diseases were clinically reviewed. This article will mainly focus on interferon therapy for malignant melanoma and cutaneous lymphoma in Japan. The cutaneous adverse symptoms that accompany interferon therapies are also discussed in this review.

Key words: Interferon; Malignant melanoma; Cutaneous malignant lymphoma; Adverse reactions

Introduction

Interferon (IFN) is used in treating various dermatological diseases. This paper focuses on the IFN therapy for malignant melanoma and cutaneous malignant lymphoma because many patients suffer from them and Japanese medical insurance covers the IFN therapy for them. The paper goes on to summarize the IFN therapies clinically studied for other diseases in Japan and foreign countries. Cutaneous adverse reactions to IFN therapies are also discussed.

Treatment for Malignant Melanoma and IFN

Malignant melanoma (Fig. 1) is a malignant tumor of melanocytes. The annual development rate of malignant melanoma in Japan is about 1.5 to 2 per 100,000 persons,[1] and the rate tends to increase.[2] Malignant melanoma is known to easily metastasize and be resistant to chemotherapy. It is also known to regress spontaneously. Therefore, investigators have considered it as a tumor with antigenicity to be treated with immune therapy. Although various therapies have been examined, including the use of BCG (Bacille bilié de Calmette-Guérin), adoptive immune therapy, vaccine therapy, and gene therapy, most of them remain at the level of basic research. IFN-β was found effective for cutaneous metastatic foci of melanoma[3] and has been widely used as a postoperative adjuvant therapy for malignant melanoma in Japan.

Malignant melanoma is classified into several disease stages by the thickness of the tumor, presence/absence of lymph node metastasis, and presence/absence of distant metastasis,

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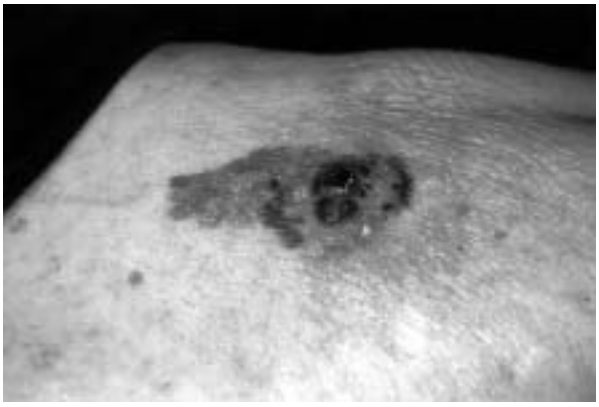

Fig. 1 Malignant melanoma

and is treated according to the stage of the disease. The American Joint Committee on Cancer (AJCC) revised the disease stage classification of malignant melanoma in 2001 (Tables 1 and 2).[4] Malignant melanoma is mainly treated with surgical excision. IFN-β is used alone or in combination with chemotherapy as a postoperative adjuvant or maintenance therapy for the disease in the IIB to III stages.[5,6] Unfortunately, no prospective study with an adequate population has been performed due to associated ethical problems and the small number of patients. However, IFN-β has been widely used as a postoperative adjuvant therapy in Japan because a basic study

Table 1 Melanoma TNM Classification[4]

T classification	Thickness	Ulceration Status
T1	≤1.0 mm	a: without ulceration and level II/III
		b: with ulceration or level IV/V
T2	1.01～2.0 mm	a: without ulceration
		b: with ulceration
T3	2.01～4.0 mm	a: without ulceration
		b: with ulceration
T4	>4.0 mm	a: without ulceration
		b: with ulceration

N classification	No. of Metastatic Nodes	Nodal Metastatic Mass
N1	1 node	a: micrometastasis*
		b: macrometastasis†
N2	2～3 nodes	a: micrometastasis*
		b: macrometastasis†
		c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	

M classification	Site	Serum Lactate Dehydrogenase
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*: Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
†: Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table 2 Proposed Stage Groupings for Cutaneous Melanoma[4)]

	Clinical Staging*			Pathologic Staging†		
	T	N	M	T	N	M
O	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III‡	Any T	N1	M0			
		N2				
		N3				
IIIA				T1-4a	N1a	M0
				T1-4a	N2a	M0
IIIB				T1-4b	N1a	M0
				T1-4b	N2a	M0
				T1-4a	N1b	M0
				T1-4a	N2b	M0
				T1-4a/b	N2c	M0
IIIC				T1-4b	N1b	M0
				T1-4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

*: Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, if should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

†: Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

‡: There are no stage III subgroups for clinical staging.

showed IFN-β locally administered to a tumor migrated through lymph ducts into the tumor-affected lymph nodes at a high concentration[7)] and because a retrospective study showed a significantly higher 5-year survival rate with DAV (DTIC [dacarbazine], ACNU [nimustine], and VCR [vincristine]) therapy plus IFN-β than with DAV therapy alone in patients with Stage III malignant melanoma.[8)]

DAV plus IFN-β therapy has been performed with the following protocol.[9,10)] DTIC is administered by intravenous drip infusion at a dose of 80 to 140 mg/m^2 for 5 days continuously. ACNU at 50 to 80 mg/m^2 and VCR at 0.5 to 0.8 mg/m^2 are intravenously administered with a side tube on Day 1. In parallel with these treatments, IFN-β is locally injected for 5 to 10 days at several intracutaneous sites around the primary surgical site at a total dose of 3,000,000 IU/body. This is considered as a single course, and repeated after withdrawal intervals of 4 to 6 weeks. This therapy is repeated for 2 to 3 courses for the IIA and IIB stages, and for 5 to 6 courses for the IIC and III stages. The maintenance therapy with IFN-β is performed, if possible, by locally injecting it to several intracutaneous sites around the primary surgical site at a total dose of 3,000,000 IU/body every 2 to 4 weeks for 2 to 3 years. Although the local injection of IFN-β

is painful, the pain can be relieved by dissolving it in 1 to 3 m*l* of a 1% procaine injection solution. No lidocaine injection solution can be used because IFN-β changes its formulation to cause clouding. Fever that may occur after the local injection of IFN-β can be relieved by administering an anti-inflammatory analgesic.

It should be noted that several cases with secondary cancer suspected to derive from DTIC or ACNU (acute myeloid leukemia and myelodysplastic syndrome) were recently reported in patients treated with the postoperative adjuvant therapy.[11] It is necessary to decide whether the DAV plus IFN-α therapy should be performed or not for patients in the II stage, and if applicable in the III stage as well, by carefully considering the patient's age, physical status, complications, and tumor thickness. Patients choose their therapy under the informed consent. Postoperative adjuvant therapy with only a local injection of IFN-β has also been examined.[9] That is, IFN-β is intracutaneously injected once daily at several sites around the surgical site at a total dose of 3,000,000 IU/body, and a course consisting of 10 injections is repeated after withdrawal intervals of 4 to 6 weeks. It is considered appropriate to perform 2 to 3 courses for the II stage disease and 5 to 6 courses for the III stage disease. The decision to choose an optimal postoperative adjuvant therapy should be made carefully, in accordance with the patient's condition.

The IV stage disease should be treated by a combination of surgical excision of localized metastatic foci, chemotherapy, BRM therapy, radiotherapy, immunotherapy, and thermotherapy. Known regimens of the BRM therapy include the CDDP + IFN-α + IL-2 therapy in which chemotherapy, IFN-α, and interleukin-2 (IL-2) are combined,[12] DTIC + BCNU + CDDP + TAM + IFN-α + IL-2 therapy,[13] and DTIC + CDDP + VBL + IFN-α + IL-2 therapy.[14] Although some investigators have reported high response rates for these regimens, the regimen most effective for life prognosis (chemotherapy alone, chemotherapy + BRM therapy, or BRM therapy alone) has not been determined. Since none of the above regimens are covered by Japanese medical insurance, the VI stage disease is often treated with DAC-TAM therapy.[15]

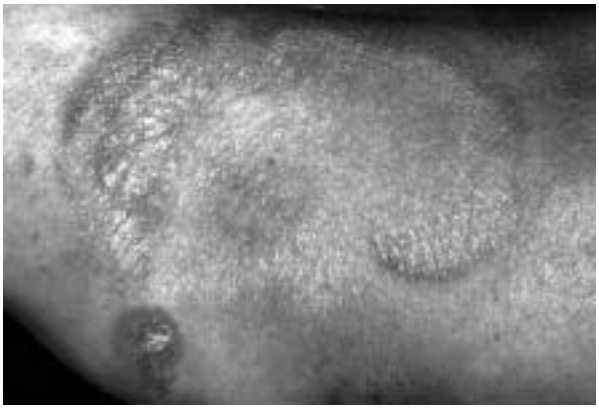

Fig. 2 Mycosis fungoides

IFN Therapy for Cutaneous Malignant Lymphoma

Several types of lymphoma cause cutaneous lesions; among these, IFN therapy is used for mycosis fungoides and adult T cell lymphoma. IFN therapy is known to be effective for skin lesions to some degree. However, IFN therapy has not been strictly evaluated for life prognosis in relation to any type of cutaneous malignant lymphoma.

1. Mycosis fungoides

Mycosis fungoides (Fig. 2) is the most frequent type of cutaneous malignant lymphoma. It is T cell lymphoma in which erythematous stage and plaque stages last for a long time, and

List of abbreviations
DTIC: dacarbazine, ACNU: nimustine, VCR: vincristine, DAV: DTIC/ACNU/VCR combination therapy, CDDP: cisplatin, BCNU: carmustine, TAM: tamoxifen, VBL: vinblastine

occasionally progress to a tumor stage. Patients with mycosis fungoides often die when the disease progresses to the tumor stage. It does not respond well to treatments. However, the disease progresses slowly before the tumor stage without causing visceral erosion. Therefore, during the erythematous stage and plaque stage, treatment is performed to prevent the disease from progressing to the tumor stage. The disease is managed by reducing tumor cells and minimizing the demerits associated with adverse reactions. So far, the disease during the erythematous stage and plaque stages has been treated with phototherapy (psoraren ultraviolet A therapy: PUVA).[16] Although actinotherapy remains important, the use of IFN alone or in combination with phototherapy has been increased since the early 1990's.[16] When the lesions of the disease extend to the whole skin, recombinant IFN-γ (rIFN-γ) is administered by intravenous drip infusion at 2,000,000 to 4,000,000 IU once daily, 3 to 5 times a week. When it is locally administered, it is administered to several sites in and around the lesion at a total dose of 200,000 to 2,000,000 IU/lesion, or 1,000,000 to 2,000,000 IU/cm^2. Natural IFN-γ (nIFN-γ) is intramuscularly injected once daily 2 to 3 times a week at a dose of 1,000,000 IU. In any case, the effectiveness of the therapy is determined at 4 weeks from the start.[17] However, there was a patient in whom skin lesions of cutaneous malignant lymphoma were successfully relieved with nIFN-γ, but subsequently extended to other organs, leading to death.[18] Although it is unknown whether the patient experienced exacerbation of the disease through its natural course or nIFN-γ changed the characteristics of tumor cells, extreme care should be exercised in using IFN, as with other therapeutic techniques. There is a protocol of IFN-α in which 3,000,000 IU/m^2 of IFN-α is subcutaneously injected 3 times weekly in combination with the oral administration of etretinate,[19] although it is not covered by Japanese medical insurance.

2. Adult T cell leukemia/lymphoma

Adult T cell leukemia/lymphoma is leukemia and lymphoma caused by HTLV-1. It is classified into 4 types, namely, acute, lymphoma, chronic, and smoldering types,[20] and the smoldering type is further divided into cutaneous and narrow sense smoldering subtypes.[21,22] It has been reported that the intramuscular injection of 1,000,000 IU of nIFN-γ once daily was effective for eruptions in patients with the cutaneous type characterized by the cutaneous infiltration of tumor cells without leukemia, tumor-induced lymph node swelling, or tumor cell infiltration to other organs.[17,23] nIFN-γ has been reported effective to some degree even in patients with cutaneous tumor or leukemia,[24] while there have been many patients including patients during acute exacerbation or with acutely progressing disease, who have not responded to IFN-γ.[17] Therefore, one should refrain from using IFN-γ in such patients.

Attempts at IFN Therapy for Other Diseases

Other diseases for which the therapeutic effect of IFN has been reported include viral verruca,[25,26] porphyria cutanea tarda,[27] cryoglobulinemia associated with type C hepatitis,[28] Kaposi's sarcoma associated with AIDS,[29] intraepidermal carcinoma, such as Bowen's disease, actinic keratosis, and Paget's disease.[30]

Cutaneous Lesions Associated with IFN Therapy

As the use of therapies involving various cytokines has advanced, it has become known that such therapies may cause cutaneous lesions.[31] The cutaneous lesions that can be caused by IFN are summarized below.

1) Erythema and skin itching: Urticaria, edematous erythema, and erythematous papula may occur in the initial stage of IFN therapy, often in a few weeks. However, IFN

therapy can often be continued with symptomatic therapy or by adjusting the dose or administration intervals.

2) Psoriasis: IFN may exacerbate concurrent psoriasis vulgaris or induce psoriasis.[32–34] Psoriasis may worsen so severely that the treatment of the primary disease has to be discontinued.

3) Alopecia: Alopecia frequently occurs with IFN therapy.[35] The incidence of alopecia ranges from 10 to 30%, depending on reports. It has been particularly frequently reported with the use of IFN-α. It often occurs 2 to 3 months after the start of IFN therapy and resolves in several months even when the therapy is continued.

4) Pigmentation and depigmentation: Several cases with pigmentation or depigmentation have been reported.[36–37]

5) Pemphigus: Pemphigus is an autoimmune disease characterized by blisters on the whole body surface. A small number of cases with the disease have been reported with the use of IFN-α or β.[38,39] The disease requires immediate treatment because it can be lethal.

6) Skin ulcers at injection site: The subcutaneous or intramuscular injection of IFN-α or β may cause ulcers at the injection site.[40–43] They may occur a while after the start of the IFN therapy, often after 6 months or later. It is inferred that IFN may exacerbate the skin ulcers. It is desirable to inject IFN intramuscularly, instead of subcutaneously, to prevent them. It is necessary to change injection sites regularly to avoid injecting IFN at the same site continuously. Although the ulcers may resolve with conservative external therapy, they may require surgical treatment when they are associated with extensive skin necrosis.

7) Others: The use of IFN has been reported to cause contact dermatitis,[44] sarcoidosis,[45] and erythema nodosum.[46]

Conclusions

IFN therapy in the field of dermatology is mainly performed for treating malignant melanoma and cutaneous malignant lymphoma. The former is treated with IFN-β used for postoperative adjuvant therapy, while the latter is treated with IFN-γ in patients in whom lesions remain at the cutaneous level and progress slowly. The DAV + IFN-β regimen is included in the standard therapies for malignant melanoma. However, IFN therapy causes various cutaneous adverse reactions. Since IFN therapy is generally used for intractable or malignant primary diseases, efforts should be made to continue it as long as skin symptoms can be controlled with symptomatic therapies or by adjusting the dose of IFN. However, extreme care should be exercised regarding cutaneous symptoms during IFN therapy, because they may threaten the patient's life.

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Practice of Interferon Therapy
—Multiple myeloma and other related hematological malignancies—

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Abstract: Practical aspects of the interfron (IFN) therapy for multiple myeloma and other neoplasms of hematopoietic organs are reviewed. While there has been no established evaluation of therapeutic responses to IFN for myeloma, recent ECOG randomized trials of multiple-drug chemotherapy with versus without IFN have reportedly demonstrated greater efficacy of the therapy combined with IFN. A multicenter collaborative study of ROAD-IN (MCNU, VCR, melphalan, dexamethasone, and IFN-α) conducted in Japan has shown favorable results. Meta-analyses of clinical trial data covering a large patient population also evidenced an increase in response rates and prolongation of responsive duration. From these studies, one can conclude that the significance of IFN in the therapeutic strategy for myeloma lies in its efficacy as a maintenance therapy regimen rather than as a single-drug induction therapy and that, if used for remission induction, IFN may more effectively be administered some way behind other chemotherapeutic regimen. IFN is used also in the treatment of such neoplasms as hairy cell leukemia or lymphoma, besides myeloma. A prospective role of IFN has been proposed in mini-transplantation.

Key words: Multiple myeloma; Interferon α (IFN-α); ROAD-IN therapy; Hairy cell leukemia

Introduction

Twenty years have passed since interferon was clinically applied to treat multiple myeloma. Only IFN-α has been used and evaluated for its efficacy when used alone or in combination with chemotherapy and for its significance when used in the induction or maintenance therapy. Although not definitely determined, the positioning of IFN-α in the therapeutic strategy of multiple myeloma is described here with recent therapeutic results. The therapeutic

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role of IFN-α for other related hematological diseases is also mentioned.

IFN-α Therapy for Multiple Myeloma

There have been many reports on the therapeutic results of IFN-α for multiple myeloma. Positive and negative reports have been repeatedly published. IFN-α regimens that had proven effective in pilot studies have often failed to show any significant effect in randomized comparative studies. The utility of IFN has also been discussed in terms of medical economics. IFN is now generally considered an important option for treating multiple myeloma probably because the disease remains lethal in spite of the advance of hematopoietic stem cell transplantation, i.e. it is often difficult to meet the eligibility for the transplantation since the disease frequently develops in elderly population, and because an acceptable therapeutic strategy has not been established yet. Before describing the practice of the treatment, let us consider the biological activities of IFN-α.

1. Action mechanism of IFN-α for myeloma cells

The use of IFN-α as a therapeutic drug for myeloma is justified from the following findings[1,2]: (1) IFN-α stimulates the cytotoxic activity of NK cells; (2) it stimulates macrophages to express major histocompatibility antigens and tumor-specific antigens associated with antigen presentation; (3) it inhibits colony formation from myeloma cells in culture; (4) it inhibits the production of M protein from myeloma cells; (5) it reduces the expression of IL-6 receptor associated with myeloid cell proliferation; and (6) it down-regulates the expression of oncogenes, such as c-myc and N-ras. Based on these findings, IFN-α has been clinically applied. However, it has also been reported that IFN-α stimulated the proliferation of myeloma cells when it was used at a low concentration.

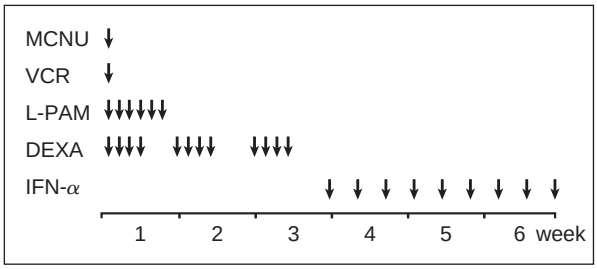

Fig. 1 Induction therapy for multiple myeloma (ROAD-IN regimen)
MCNU (ranimustine): 40 mg/m^2, i.v., day 1, VCR (vincristine [Oncovin]): 1.2 mg/m^2, i.v., day 1, L-PAM (melphalan [Alkeran]): 8 mg/m^2 p.o., days 1 to 6, DEXA (dexamethasone): 40 mg/body p.o. (i.v.), days 1 to 4, 9 to 12, 17 to 20, IFN-α (interferon-α): 2,000,000 units/m^2 (max: 3,000,000 units/body) sc, days 20 to 42 (thrice/weekly)

2. Induction therapy with IFN-α

Although randomized comparative studies initially failed to demonstrate the superiority of IFN-α, results indicating its effectiveness have recently become available.

(1) ECOG study

The Eastern Cooperative Oncology Group (ECOG) performed a phase III clinical study in untreated patients to compare complete response and survival rates between the VBMCP (vincristine, BCNU, melphalan, cyclophosphamide, and prednisolone) regimen and the regimen plus either IFN-α, or high-dose cyclophosphamide.[3] IFN-α was administered at a dose of 5×10^6 units/m^2 thrice weekly from Day 22. The results obtained from 628 subjects showed a significantly higher CR rate in the VBMCP + IFN-α group than the VBMCP group (18% vs. 10%). Although no significant difference was noted for survival rate, the response duration was significantly longer in the VBMCP + IFN-α group. Further, the VBMCP + IFN-α group fared better than the VBMCP + high-dose cyclophosphamide group in relation to complications from serious infections. ECOG concluded that the VBMCP + IFN-α regimen was especially effective in elderly patients and for IgA-type myeloma.

(2) Japanese multi-center joint study

Similar results have been reported in Japan.

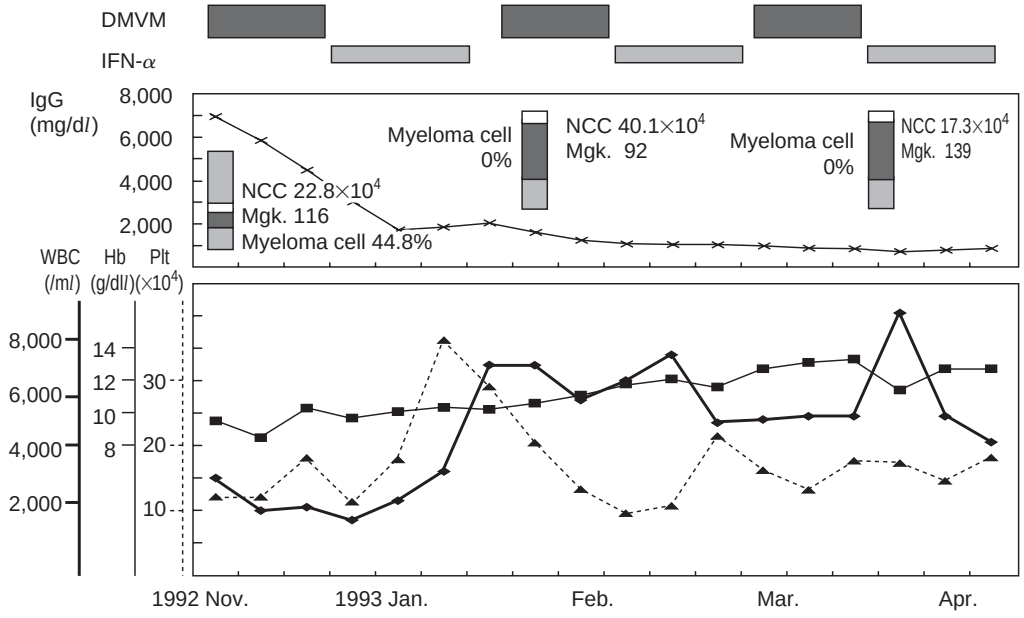

Fig. 2 Clinical case of a 72-year-old male patient with multiple myeloma

A study on induction/maintenance therapy with IFN-α was started in 1991 as being funded by the Foundation of Inter-disciplinary Therapies Studies.[4] Figure 1 shows the regimen used in the study. IFN-α was administered thrice weekly from Days 22 to 42 after MCNU (ranimustine), vincristine (Oncovin®), melphalan (Alkeran®), and dexamethasone were administered. Maintenance therapy with 2×10^6 units/m^2 (up to 3×10^6 units/m^2) of IFN-α was performed until the disease recurred. The study was undertaken as a single-arm pilot study including 161 patients, and resulted in a CR rate of 24%, PR rate of 51%, and median survival period of 3.6 years. The survival period was 4.3 years in patients with CR or PR.

However, the study concluded that no significance could be offered for the maintenance therapy with IFN-α. The regimen used was named the "ROAD-IN" regimen (ROAD-IN being an acronym formed from the initials of the drugs used). The protocol was based on the DMVM-IFN-α therapy which had been originally developed by Kitani, T. *et al.*[5] in the Hanshin Myeloma Study Group. Although IFN-α was initially administered for 20 days from the day when the drugs were started, the duration was subsequently reduced to 12 days. A CR rate of more than 25% was obtained.

Our Kinki University group took part in these studies from the start. The results were excellent, with 46.4% (13 patients each) of CR and PR rates in 28 patients treated with the DMVM-IFN-α or ROAD-IN therapies. The overall survival rate in the CR patients (as determined by the Kaplan-Meier method) reached a plateau of about 60% at 5 years. Figure 2 shows a representative case: although the M protein was 7,000 mg/d*l* at hospitalization, it returned to the normal range in about 2 months.

(3) Other multi-drug combination regimens

Other multi-drug combination regimens with IFN-α include the VAD-IFN-α regimen including vincristine, adriamycin, and dexamethasone, VMCP-IFN-α regimen including vincristine, melphalan, cyclophosphamide, and prednisolone, and PACB-IFN-α regimen including prednisolone, adriamycin, cyclophosphamide, and BCNU. The regimens resulted in CR rates ranging from 1 to 30%, median remission periods from 12 to 26 months, and median sur-

Table 1 Meta-Analyses of the Effect of IFN on Multiple Myeloma[9]

	Significant effects in groups treated with IFN	
	Ludwig & Fritz	Oxford group
Induction therapy		
Response rate	Increased by 6.6%	Increased by 4.4%
Response period	Prolonged by 4.8 months	Prolonged by about 6 months
Survival period	Prolonged by 3.1 months	Prolonged by about 2 months
Maintenance therapy		
Response period	Prolonged by 4.4 months	Prolonged by about 6 months
Survival period	Prolonged by 7.0 months	Prolonged by about 7 months

(*Acta Oncol* 2000; 39: 815–821)

vival periods from 32 to 52 months.[6]

3. Maintenance therapy with IFN-α

Contradictory results have been reported for the efficacy of the maintenance therapy with IFN-α. Many investigators claim that IFN-α should be used for maintenance therapy rather than induction therapy because myeloma cells stop the proliferation and reach a plateau phase after remission is achieved and IFN-α is also effective for the cells in the G0 stage that have not entered the cell cycle. The Southwest Oncology Group (SWOG) compared the recurrence-free survival period between IFN-α alone and IFN-α plus prednisolone in patients who achieved remission with the VAD regimen, and reported that the latter regimen was superior.[7] The median progression-free survival period was 9 and 19 months in the IFN-α and IFN-α + prednisolone groups, respectively ($p = 0.008$). They made the comparison under the idea that the maintenance therapy with IFN-α was significantly effective. The median overall survival period was not significantly different (46 vs. 57 months).

Futhermore, a study reported that remission was clearly more prolonged in a group treated with the induction and maintenance therapies using IFN-α than in a group not treated with the IFN-α-containing regimen (median remission period: 21.2 vs. 6.4 months).[8]

4. Meta-analysis of IFN-α therapy for multiple myeloma

The efficacy of IFN-α has been analyzed according to evidence-based medicine. What is most valuable in the analysis is the meta-analysis that compares the results of several large-scale prospective randomized comparative studies. Ludwid *et al.*, who examined 3,948 patients from 30 randomized comparative studies,[9] showed that significantly higher CR, PR, and overall survival rates could be achieved in the IFN-α + chemotherapy group than the chemotherapy group, although the differences were marginal.

An Oxford joint study group of myeloma trialists also performed a meta-analysis in 4,012 patients from 24 randomized studies. The result demonstrated that IFN-α moderately improved recurrence-free and overall survival rates.[10] It is therefore considered that individual studies failed to show any significant difference possibly due to the small number of patients examined. Table 1 shows the results of the meta-analyses.

5. Adverse effects of IFN-α therapy

In the treatment of multiple myeloma, IFN-α causes adverse effects similar to those observed in other clinical fields. The ROAD-IN regimen caused leucopenia in 72% of the cases, thrombocytopenia in 15%, fever in 26%, and malaise in 49%.[4] None of these adverse

effects was serious. The type and frequency of adverse effects are similar in other reports. Since IFN-α dose-dependency causes adverse effects, some patients refused to receive it at a dose of 3×10^6 units or higher: the second course of IFN-α had to be discontinued in a small number of patients.

IFN-α Therapy for Other Hematopoietic Diseases

IFN-α has been used to treat not only multiple myeloma, but also low-grade malignant lymphoma such as follicular lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia. IFN-α has also been reported for the treatment of pre-leukemic myelodysplastic syndrome. However, IFN-α has not been so frequently used as for myeloma, and the efficacy for those diseases has not been established. The use of IFN-α for only hairy cell leukemia is covered by Japanese medical insurance. IFN-α is not considered as the first line therapy for these hematological diseases in most medical institutions. It is not highly rated even in the few institutions where it does come into consideration as the first line therapy. However, it is possible that IFN-α will play a significant role in combination with other drugs.

Conclusions

The efficacy of therapeutic regimens for multiple myeloma has been systematically evaluated since the MP regimen (melphalan and prednisolone) was clinically applied. Since then, many multi-drug chemotherapy regimens have been attempted, but none has become standard for the disease. Chemotherapy regimens including IFN-α have been unsatisfactory as well. At the present, IFN-α is evaluated as a therapeutic drug for multiple myeloma as follows: (1) IFN-α is not useful when used alone; (2) many investigators think that it should be used for maintenance therapy rather than induction therapy; and (3) it is effective in induction therapy only when it is combined with multi-drug chemotherapy regimens, and is more effective when its administration is delayed. Although the meta-analyses indicate that IFN-α is an important and useful drug in the treatment of multiple myeloma, evaluations of its usefulness will be modified.

Stem cell transplantation conditioned with non-myeloablative regimen has been rapidly progressing in various fields. This kind of transplantation targets patients for whom the conventional transplants have not been indicated due to the higher age and the complications affecting performance status, and the majority of patients with multiple myeloma could be included in the target for this mini-transplantation. It is expected to become a promising therapy for relatively elderly patients of 50 or older. IFN-α may play a role in the new therapeutic modality.

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Olfactory Disturbances
—Pathophysiological findings and the development of new therapeutic procedures—

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Abstract: Chronic rhinosinusitis is the most frequent cause of hyposmia. We established a new experimental animal model to investigate pathological findings in the olfactory epithelium and olfactory bulb of rats and describe the possible etiology of hyposmia due to rhinosinusitis. Not only dysfunction of the olfactory epithelium but a central type of hyposmia caused by disorders of the olfactory bulb was demonstrated by immunohistochemistry. The possible etiology of hyposmia after common colds and dysosmia after traumatic olfactory disorders is also described based on recent studies. Hyposmia after common colds is strongly associated with nasal obstruction, swelling of the nasal mucosa, and edema of the mucosa of the olfactory cleft observed by nasal fiberscopy. Viral infection is considered one of the etiologies of anosmia after common colds, especially in women from 40 to 60 years old, and results in a poor outcome. One possible explanation of olfactory dysosmia is misdirected connections during reinnervation of the olfactory bulb by olfactory nerve fibers after apoptotic change of olfactory receptor neurons and traumatic amputations of olfactory filla at the level of ethmoid lamina cribrosa. These findings suggested new ideas for the treatment of patients with different types of olfactory disturbances.

Key words: Pathophysiology; Olfactory disturbances; Paranasal sinusitis; Common cold; Parosmia

Introduction

The research on gustatory and olfactory senses have not been fully developed as compared to those on visual and auditory functions. Yet these senses contribute significantly to one's QOL in everyday life. Due to hearing difficulty, aged people tend to be isolated from their communities and also from participating in social activities. Considering these aspects, gustatory and olfactory disturbances among them may interfere with their desire to live and enjoy

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their lives.

At the beginning of the 21st century, our aging society continues to be complex and faces further problems to be solved. The pathophysiological elucidation of various olfactory disturbances and the development of new therapeutic methodology are much desired. The current situation is presented in this literature.

Chronic Paranasal Sinusitis

Paranasal sinusitis is the most frequent cause of olfactory disturbances in Japan.[1)] It is true that sequential changes that occur at the olfactory mucosa caused by paranasal sinusitis have not been investigated sufficiently. Nor have appropriate animal models been found that are suitable for such studies. Therefore, we prepared a model for experimental paranasal sinusitis by using rats to elucidate the mechanism by which olfactory disturbances develop and to conduct histological observations of the olfactory epithelium and olfactory bulb.[2)]

1. Pathophysiology

(1) Olfactory disturbance (direct effects of sinusitis)

A foreign material (polyvinyl acetal) coated with *Staphylococcus aureus* was inserted into one of the nasal cavities of rats and 3, 7, 14, 21, and 28 days later, samples from the nasal cavity and olfactory bulb were collected (from 10 animals at each experiment) to prepare coronal sections. HE stain was applied to the samples from the nasal cavity to examine the maxillary sinus and ascertain the onset of paranasal sinusitis.

The HE-stained nasal sinus section obtained from the rats affected by paranasal sinusitis was used to measure the thickness of the olfactory epithelium. The sections from the nasal cavity of the rats with paranasal sinusitis were used for immunohistological observation of the olfactory epithelium by using the following antibodies: anti-protein gene product 9.5 (PGP9.5) antibody, anti-proliferating cell nuclear antigen (PCNA) antibody, anti-single-stranded DNA (ssDNA) antibody, and anti-inducible nitric oxide synthase (iNOS) antibody. To ascertain the presence (or absence) of changes to the central olfactory system, an immunohistological study was conducted on the olfactory bulb samples of the rats affected by paranasal sinusitis by using an anti-tyrosine hydroxylase (TH) antibody.

The results of these observations may be summarized as follows: The onset of paranasal sinusitis was confirmed in 6 animals after 3 days, 7 animals after 7 days, 6 animals after 14 days, 6 animals after 21 days, and 7 animals after 28 days following exposure to *Staphylococcus aureus*. Inflammation developed in the olfactory epithelium that was affected by paranasal sinusitis within 3 days and the inflammatory condition persisted even after 28 days. The thickness of the olfactory epithelium, the number of olfactory cell layers, and the count of the olfactory cells per $100\mu m^2$ of the olfactory epithelium continued to be markedly reduced until after 21 days. The olfactory neurofibril bundles became elongated and scarce in proportion to the time (i.e., number of days) that the foreign body was retained in the nasal cavity. The olfactory cell regenerating activity was markedly reduced for the initial 7 days and hardly recognized on the 21st or 28th day. Apoptosis of the olfactory cells was most pronounced on the 3rd and 7th days, after which the activity was reduced and became barely recognizable on the 21st or 28th day. The iNOS expression in the olfactory epithelium was hardly noted in the normal olfactory epithelium. The enzyme expression was abundant around the basal cells of the samples obtained from the animals with paranasal sinusitis; but it was somewhat reduced where the olfactory epithelium had undergone marked degeneration. In the olfactory bulb, the TH expression of the juxtaglomerular cells began to be reduced on the 7th day and became much reduced on the 21st and 28th days.

It has been shown for the first time that in

addition to the olfactory epithelium, histological changes develop in the olfactory bulb and central olfactory disturbances may occur in chronic paranasal sinusitis.

(2) Olfactory disturbance (indirect effects of sinusitis)

Inflammatory changes in the olfactory cleft, nasal polyps, especially those of the olfactory cleft, and excessive secretion that are caused by sinusitis have been pointed out. It is well known that these conditions are also accompanied by morphological deviations of the nasal cavity, such as accentuated curved nasal septum and nodules of the nasal septum. The pathophysiology of olfactory disturbances caused by chronic paranasal sinusitis may therefore be summed up as the so-called mixed olfactory dysfunctions, where the aforementioned olfactory epithelial changes and respiratory olfactory dysfunction — due to deviations in air flow within the nasal cavity — are involved.

2. Treatment

Needless to add, the treatment of chronic paranasal sinusitis, the cause of olfactory disturbances, also constitutes the basis of treatment of the latter.

(1) Surgical treatment

Surgical correction of morphological deviations of the nasal cavity — e.g., modification of the nasal septum, excision of the turbinate, and elimination of nasal polyps — and endoscopic surgery of the paranasal sinus are effective in improving respiratory or mixed olfactory disturbances. However, complete recovery from extensive and multiple polyps is difficult. It has been reported that the recovery rate is about 50%.[3)]

(2) Drug therapy

(i) Nasal instillation, nasal spraying, or local injection of adrenal cortex hormones

With the patient in the head-down (chin-up) position, 1 to 2 drops of a 0.1% solution of betamethasone sodium (Rinderon®) are instilled in the nasal cavity 3 to 4 times a day, during which time the patient is instructed to hold the position for about 5 minutes. If no improvement is seen within one month, the medication is discontinued. When the patient is unable to hold his head in the specified position or he has chronic sinusitis or has recently undergone surgery, the same preparation is sprayed from an atomizer twice a day. Topical application of 2 mg/0.5 m*l*V of dexamethasone or 40 mg/1 m*l*V of methylprednisolone to the olfactory mucosa is also recommended. Both are applied once every 2 weeks and repeated 4 to 6 times.

(ii) Oral medication

Recently, long-term application of a small amount of macrolide antibiotics has been recommended as a conservative or postoperative adjuvant therapy for chronic paranasal sinusitis. This medication is usually combined with ethyl L-cysteine hydrochloride (Cystanin®) or L-carbocysteine (Mucodyne®).

(iii) Therapeutic modalities projected in the near future

For the etiology of chronic paranasal sinusitis, it has been proven that inflammatory cytokines (e.g., IL-1β, TNF-α, GM-CSF, and IL-6) are involved. Therefore, much is expected from gene therapy to control the genes responsible for the expression of these cytokines at the genetic level or chemotherapy targeted at these genes.

Olfactory Disturbances Following a Common Cold

It is understood that olfactory disturbances complicating upper respiratory inflammation are caused by nasal occlusion, swelling of the nasal mucosa, or edema of the mucosa of the olfactory cleft. Most of these symptoms are transient, being eliminated in 2 to 3 days. However, in some instances they may develop after a cold and their prognosis is considered to be poor. The condition frequently affects women between 40 to 69 years of age.[4)] The question of the exaggerated susceptibility to infection by viruses from the olfactory nerve and the resistance to recovery from disturbances in this

age range, as well as the higher frequency of occurrence among women, have not been fully elucidated.

1. Pathophysiology

Excessive secretion or dryness of the olfactory mucosa and ciliary dysfunctions of the olfactory cells due to acute inflammation and subsequent secondary infection following viral diseases may explain the development of olfactory disturbances. Histopathological findings from the material obtained by a biopsy of the olfactory mucosa were presented by Tomlinson,[5] who cited central nervous dysfunction via the olfactory nerve, and by Yamagishi,[6] who called attention to a reduction in the number of olfactory cells.

2. Treatment

For peripheral or central olfactory disturbances, vitamin B_{12}, vitamin A, and adenosine triphosphate (ATP®) are commonly used. There is a report that extols the favorable effect of Oriental medicine (e.g., Toki-Shakuyaku-San and Keishi-Bukuryo-Gan).[7] Sometimes the serum zinc content is reduced, with rapid loss of the gustatory and olfactory sensations and a resultant acute loss of taste for food. Whether the state is acute or chronic, it has been pointed out that reductions in the serum zinc level results in anorexia and gustatory and olfactory disturbances. It is not certain why a drop in the serum zinc level triggers these symptoms. In the brain, the zinc content is at the highest in the hippocampus, followed by the cortex, stria, and cerebellum. It is also known that zinc exists at a high concentration at the terminals of the mossy fibers of the cerebellum and hippocampus, suggesting that zinc is involved in the functioning of the central nervous system.[8]

Parosmia

If a loss or reduction in the olfactory function represents quantitative deviations of olfactory functions, parosmia is typical of qualitative disturbances of the same function. In clinical patients, parosmia may be found in olfactory dysfunctions following a cold (mentioned earlier) and following trauma suggestive of disruption of the olfactory fibers. Characteristically, parosmia develops after some time has elapsed, instead of immediately after olfactory dysfunctions.[9]

1. Pathophysiology

Instead of remaining viable throughout one's life, the olfactory cells die after a certain time, repeating regeneration through division and proliferative processes.[10] Specifically, the old cells are replaced by new olfactory cells that are generated by division of the stem cells of the basal layer so that the axons of new olfactory cells may constantly project to the olfactory bulb.[11]

According to a recent finding, the site of the olfactory bulb to which the axons of olfactory cells project is well preserved in individuals and remains constant throughout one's life. In other words, the axons that have newly developed accurately recognize the sites on the glomeruli: by projecting toward these sites, the "olfactory map" on the olfactory bulb is continually being recreated and maintained.

In parosmia, however, it is understood that axonal projection occurs at different sites on the olfactory bulb following regeneration.[12] An olfactory stimulus may be detected by reprojection through neural regeneration but projection to a different site results in the perception of a different type of olfactory stimulus.

2. Treatment

The current therapeutic modalities are generally similar to those applied to the peripheral and central olfactory disturbances described above. In addition, administration of vitamin A, which is known to affect differentiation and proliferation of the olfactory epithelium, has been reported. Leopold, *et al.* ruled out the efficacy of vitamin A: instead they cited a case of parosmia in which unilateral excision of the

olfactory mucosa was found to be effective.[13] They attributed the improvement of the symptom to appropriate nerve projection pathway but this case is somewhat unique and follow-up studies are needed to prove the validity of the procedure.

3. Therapeutic procedures for the near future

Apoptotic death of the olfactory cells has been observed in the early stage following disruption of the olfactory fibers in experiments using mice and rats. It was proven that the number of olfactory cells and the thickness of the layer of these cells are reduced; but within 3 to 4 weeks, regeneration of these cells is completed, thus restoring the olfactory activities and functions. It is readily conceivable that similar processes take place in man. Prognosis is poor in those clinical patients who suggest disruption of their olfactory fibers: the olfactory function cannot be restored in most of these patients.

For the cause of parosmia, incomplete connection between olfactory fibers and the olfactory bulb — in spite of the regeneration of the olfactory cells — is considered. It is believed that the formation of granulation tissue around the lamina cribriform is the most significant disturbance. Therefore preventing the formation of granulation tissue at the site noted above or enabling the neural connection in spite of the presence of the granulation tissue will lead to the development of new therapeutic approaches.

In Closing

Recent pathophysiological findings on chronic paranasal sinusitis (a condition most often cited as the cause of olfactory disturbances in Japan), olfactory disorders consequent to the common cold, and parosmia were presented. Trends in the therapeutic modalities projected in the near future (including gene therapy) were also introduced.

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Treatment of Housewives' Hand Eczema
—Touching on recent topics—

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Abstract: The clinical features of housewives' (hand) eczema are described, distinguishing between dry and moist forms and the pathogenic factors and mechanism of each form, based on the past three years of patient data from practice at Tokyo Kosei Nenkin Hospital. I will also introduce the recent understanding of characteristics of the hands and the barrier function of the stratum corneum, and describe their relevance to the treatment, prevention, and education in skin care of this condition, touching on recent topics.

Key words: Housewives' eczema; Hand eczema; Stratum corneum barrier; Moisture-retentive agent; Topical steroid

What is Housewives' Eczema?

In current usage, the term "housewives' eczema" is synonymous with "hand eczema," which is popularly called "sore hands" or "chapped hands". This skin disease is a type of eczema or dermatitis. Among all parts of the human body, the hands are most frequently exposed to challenging chemicals and environmental conditions. Therefore they are the area most susceptible to skin problems. This term has been used at home and abroad because its incidence is so high among housewives, who have to use their hands frequently during domestic tasks, and in this group it is commonly chronic, recurrent and uncontrollable. In addition to housewives, others who develop occupational hand eczema include barbers, hairdressers, healthcare personnel, cooks and other food/drink-related service providers, cleaners, and office workers who deal with papers or bills. This disease is commonly seen in dermatology clinics.

In this paper, I will focus on non-occupational housewives' hand eczema and refer to some recent topics relevant to this disease.

1. Statistical aspect

Although the overall clinical incidence of hand eczema, including housewives' hand eczema, has been reported in some Japanese and foreign literature, the actual incidence is

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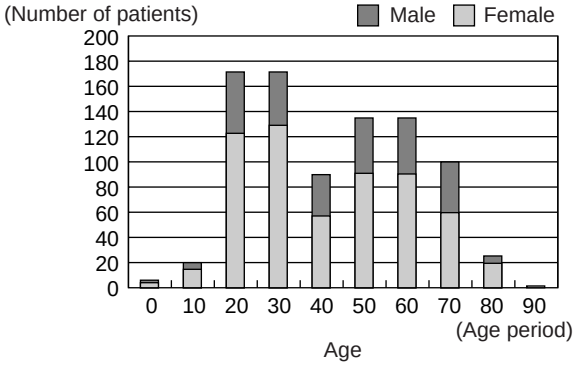

Fig. 1 Number of patients presenting with hand eczema for the past three years by age

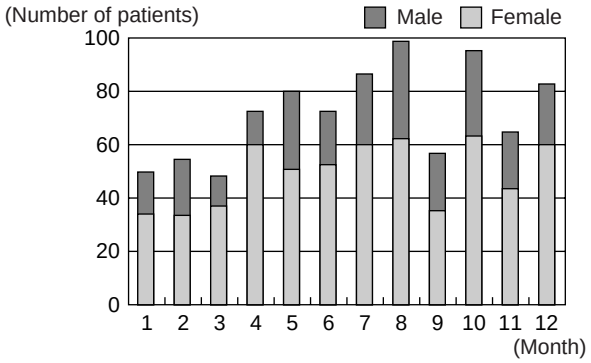

Fig. 2 Number of patients presenting with hand eczema for the past three years by month

unknown. Over 30 years ago (1965), the Lund University (Sweden) department of dermatology conducted a study involving 4,633 patients. The researchers found that the hands were affected in 34% of all patients seen at the department of dermatology, that more than half of these patients had hand eczema, and that women outnumbered men by a ratio of 2 to 1.[1)] In Japan, the statistics on patients who visited the Shimane Medical University (Department of Dermatology) for the past 15 years were reported by Jidoi five years ago. According to his report, consistently about 8% of all outpatients had hand eczema, and women outnumbered men by approximately 4 to 1.[2)] In the department of dermatology of our hospital located in the center of Tokyo, about 5% of all new outpatients seen in the past three years (from 1999 to 2001) had the disease, with a male/female ratio of 1 : 2.3. The incidence was highest in women in their 20s and 30s, and was also high in patients in their 50s and 60s, followed by patients in their 70s (Fig. 1).

Figure 2 shows the number of patients who visited our department by month. More patients visited in the seasons from spring to autumn (April to October) except September and in December, suggesting a trend similar to the report by Jidoi indicating that the lowest number of patients visited in January and September. Focusing on the number of female patients, a similar trend was observed: the total number was not higher in winter, except for the dry form of the disease described later. Also, 16% of all patients with eczema and dermatitis (other than atopic dermatitis and seborrheic dermatitis) presented with hand eczema. One-fourth (24%) of these patients were female.

Although simple comparisons cannot be drawn among these results, I have formed the following broad impressions: that the large proportion of outpatients presenting with hand eczema in the past has recently decreased by half although the absolute number of patients with hand eczema has not decreased, that the incidence is more than 2 times higher in females than males in all ages, that women who live in rural areas are likely to develop the condition at nearly twice the rate of those who live in urban areas, and that a higher number of patients visit hospitals in the months or seasons with high levels of activity compared to winter. In conclusion, the onset of hand eczema may be related to two factors, gender and life habits.

2. Clinical features

In practice, both dry and moist forms of the disease are mixed in a given patient. The disease alternately exacerbates and remits and, in quite a few cases, may become chronic. Rough categorization into dry and moist forms facilitates understanding the clinical features of

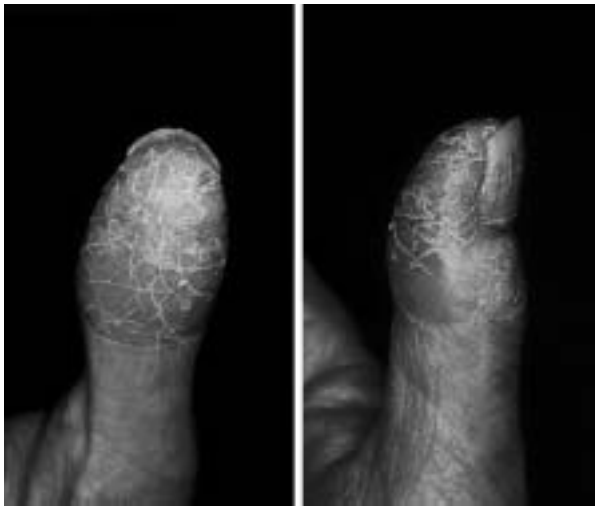

Fig. 3 Dry-form (KTPP) housewives' eczema
Keratotic inflammation presents as disappearance of fingerprints and gloss. Such inflammation frequently involves the entire area around the distal phalanx, often associated with abnormal nail growth (79-year-old patient).

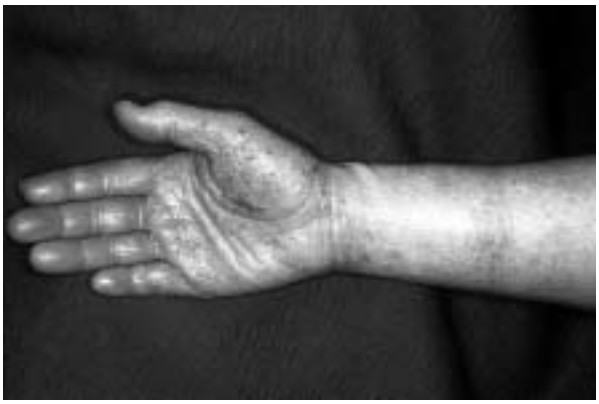

Fig. 4 Moist-form housewives' eczema
The eczema occurs acutely and is associated with severe itching and inflammation. The forearms and dorsal hands are also affected. In many cases, an allergic mechanism is suggested (43-year-old patient exacerbated by rubber gloves).

housewives' eczema.

a. Dry form (Fig. 3)

In Japan, this form of housewives' eczema has been referred to as keratodermia tylodes palmaris progressiva (KTPP),[1] and originates from the tips of the first, second and third fingers (thumb, index and middle fingers) of the dominant hand and progresses centripetally. Left untreated, the disease involves other fingers, and finally all fingers of both hands. Hyperkeratosis or exfoliation with gloss and redness in the fingertips appears, frequently accompanied by the disappearance of fingerprint patterns. In this case, fissures and pain are apt to occur. Coverage with an adhesive bandage such as a Band Aid as first aid causes inflammation, leading to further exacerbation. This is the stage when many patients visit hospitals for the first time. Deformations of the nails, such as vertical and horizontal lines and roughness are commonly observed because the entire fingertip is affected, suggesting that the condition has become chronic.

Itching is mild and rarely involves the back of the finger other than the end phalanx. Once developed, the disease frequently relapses and becomes chronic. It tends to occur and exacerbate particularly in winter. According to the statistics presented by Jidoi, 98% of the patients with KTPP were female and the disease occurs in winter at higher incidence.[2]

b. Moist form (Fig. 4)

In the moist form of housewives' eczema, severe itching and redness/inflammation as well as the appearance of small vesicles and effusion are observed. The backs of hands and fingers are frequently affected, in addition to the palms. Since this disease develops acutely, many patients presenting with this disease visit hospitals at an earlier stage. Some patients visit hospitals because the skin under a ring is affected and the resultant inflammation does not allow the ring to be removed. Some combination of irritative dermatitis due to detergents and other agents and delayed allergy to nickel or rubber gloves is indicated. Unlike the dry-form eczema KTPP described in the previous section, the moist form is observed throughout the year.

3. Pathogenic factors and mechanism

Pathogenic factors of housewives' eczema appear to include both endogenous and exog-

enous factors. Endogenous factors include atopic predisposition, and local hyperidrosis. Patients who have these predispositions are thought to have a higher incidence of hand eczema.[3] According to a questionnaire investigation of 6,666 twins two years ago by Bryld *et al.* (Denmark), hand eczema occurs in identical twins with nearly double the incidence seen in pairs of fraternal twins; however, any predisposition is related to the onset, though whether it is atopy or contact allergy is unknown.[4] However, this hypothesis is debatable and we cannot know whether either of these factors is essential.

a. Dry form

The dry form of hand eczema (KTPP) is an irritative and nonallergic contact dermatitis. The disease is initiated in two steps. The first step is the removal of skin surface lipid (delipidation) in the course of domestic chores that may involve frequent hand washing with soap, detergent and hot water, repeated use of alcohol cottons or organic solvents such as acetone and benzene, and frequent contact with newspapers or other papers. The second step is exposure of the skin to different chemicals involved in these domestic tasks. Therefore this type of eczema can occur in anyone who encounters these conditions. Chemicals such as surfactants can denature protein.[1]

b. Moist form

The moist form of eczema may occur primarily due to allergic contact dermatitis. The disease develops only in individuals who are sensitive to certain substances, and each patient seems to respond to a specific sensitizing substance. The variety of sensitizing substances is wide. Commonly encountered sensitizing substances for housewives' eczema include metals such as nickel, chromium, and cobalt, perfume, hair-dye, permanent wave liquid (especially type 1), and rubber or synthetic gloves. The range of known causative agents is now expanding to foods, including spices, and gardening-related substances. Also, contact urticaria (immediate allergy) has been caused by fresh seafood and the latex protein in natural rubber gloves, which can exacerbate housewives' eczema. When there is a suggestion that these allergic mechanisms may be involved, an aggressive search for the causative agents is necessary, using patch or prick tests.

Understanding the Characteristics of the Hands and the Barrier Function of the Stratum Corneum

1. Characteristics of the hands

The palms have a peculiar skin structure, which is related to the fact that the hands are the body part most frequently exposed to external stimuli. The stratum corneum of the palms consists of approximately 50 layers, and is much thicker than the skin on other parts of the hands (about 15–20 layers). Also unlike the facial skin, the stratum corneum has no hair follicles and sebaceous glands. In areas where hair follicles are present, the super surface lipid membrane overlying the stratum corneum is predominantly produced by the sebaceous glands associated with hair follicles, while in the palms and soles the membrane is composed exclusively of lipid produced by metabolism of epidermal cells. The super surface lipid membrane is well developed in the face, whereas the membrane in the palm is thinner, which is compensated for by a thick stratum corneum. Additionally we should understand that the back of the finger's distal phalanx has no hair follicles and that the nail margins and fingertips have the same properties as the palms and finger-pulps.

2. Barrier function of the stratum corneum

It has been shown that homeostasis of barrier function of the stratum corneum is maintained primarily by three factors; 1) surface lipid, 2) intrinsic hydrophobic lipid of the stratum corneum such as ceramide, and 3) natural moisture-retentive factors. Among these factors, ceramide has recently emerged as an important contributor to the moisture-retentive barrier.

Table 1 Housewives' Hand Eczema: Main Points of Treatment and Prevention

	Treatment	Prevention (daily life education)
Dry (KTTP)	moisture-retentive agents (urea and heparin preparation)	• Protection of hands Limit the frequency of hand washing: 2 to 3 times per day Wear two different gloves (or skin protective cream) Adjust domestic tasks (sharing among family members and automatic dishwasher) Wear gloves to protect against low temperatures • Avoid factors* leading to exacerbation * Detergent and soap, organic solvents, paper, hair-dyeing at home, metal rings, covering fissures with Band Aids
Moist	topical steroids (medium or high potency) and oral antipruritic drugs moisture-retentive agents after improvement	

Ceramide is the hydrophobic lipid that bridges the gap between the horny cells and forms the barrier that keeps water from passing through.[5] The substance is supplied by a structure of the epidermal cell called a lamellar granule (or Odland body), and the process of its metabolism and production is under investigation.[6] The so-called natural moisturizing factors are thought to bind with water within the horny cells and play a role in enhancing the flexibility of the keratin. The factor originates from the keratohyaline granules of the epidermal cells, which are the soluble amino acids produced by degeneration of fillagrin. In the cosmetics industry, great importance is placed on this factor.

When the super surface lipid membrane and lipids such as ceramide between the horny cells are removed by artificial causes, internal water is lost from the stratum corneum (transepidermal water loss [TEWL]) and the way is left open for chemical stimuli or external substances including allergens and microorganisms to invade the body, leading to susceptibility to inflammation and allergic sensitization. If scratching also occurs (itch-scratch cycle), such entry and inflammation are promoted, causing the chronic disease picture involving the two clinical forms of eczema described previously. The body part most vulnerable to the influences that permit this sequential process is the hands.

Treatment and Prevention of Housewives' Eczema (Table 1)

1. Treatment

Dry-form (KTPP) eczema is treated primarily with topical moisture-retentive agents and education in skin care. Although topical steroids (ointment or tapes) may be concomitantly used for a short time (about a week) during the inflammation phase, moisture-retention and education are very important. Emollients and moisturizers are known as moisture-retentive agents; the emollient softens the stratum corneum and the moisturizer, in addition to its softening effect, aggressively binds to water and thereby inhibits evaporation of water over a long period. Typical emollients and moisturizers are petrolatum and topical agents containing urea or heparin, respectively. Physicians should advise patients not to apply Band-Aids or other adhesive bandages to painful fissures. Instead, medical dressings can be used to cover the fissures for a short period.

Severe inflammation and itching is associated with moist-form hand eczema. Therefore medium or high potency topical steroids should be used aggressively. Additionally, a short-term coating with zinc ointment should be used for protection. Oral antihistamine should be used concomitantly to suppress itching and scratching. After the lesions have improved, these agents are replaced with moisture-retentive

agent and skin care education is started.

Some reports have shown that oral disodium cromoglycate (Intal®) is effective in patients whose nickel allergy is confirmed and worsened by dietary intake of nickel. Therefore this therapy may merit a trial.[7)]

A recent study on long-term intermittent therapy with topical steroids in patients with refractory eczema in Denmark has been reported.[8)] In this study, 120 such patients were assigned to one of three treatments: 1) topical steroid on alternate days for 3 weeks, 2) topical steroid on Saturday and Sunday, or 3) moisture-retentive agent and a non-steroid. Treatment with topical steroid on alternate days for 3 weeks showed the highest effectiveness (83%). In this study, mometasone furoate cream (released as Flumeta cream® in Japan) was used as the topical steroid.

A study conducted in Germany achieved a reported efficacy rate of approximately 90% in 28 patients using local warm bath therapy and PUVA (psoralen ultraviolet A) administered 4 times per week up to a maximum of 25 times. This therapy was recommended for refractory eczema due to a lower incidence of side effects, including phototoxic reactions, compared with conventional topical PUVA therapy.[9)]

2. Prevention and daily life education

In treating and avoiding both dry and moist eczema, patients must receive education on the need to modifying their daily lives so as to reduce the frequency of hand washing and to avoid lipid-removing irritants and allergens.

We often find a considerable reduction of the frequency of hand washing results when the patient can achieve some distance from domestic tasks, for example with travel. It is a well known fact that turnover of the stratum corneum takes two weeks. The authoritative *"Fisher's Contact Dermatitis"* states that the preferred frequency of hand washing is 2 to 3 times per day,[10)] which is, however, impractical. It has also been reported that switching from synthetic detergent to liquid soap does not modify the degree and incidence of sore hands.[11)] Therefore the use of double gloves, where cotton gloves are worn under rubber, vinyl or plastic gloves has conventionally been recommended.

Rubber gloves are known to cause delayed allergy due to the different vulcanization accelerators used in the manufacturing processes. Natural rubber gloves are reported to cause this type of allergy as well as contact urticaria due to latex protein, which can initiate an anaphylactic reaction potentially leading to death.[12)] The powder used to lubricate the interior of gloves has been suggested as a cause of rash, and there is a potential additional risk of contact allergy from powders that have absorbed latex protein, and risk of anaphylactic shock resulting from inhaling the powder.[12)] Recently a variety of gloves for medical use, including gloves with antigen removed, hypoallergenic gloves, powder-free gloves, and urethane gloves, have become commercially available.[13)] Patients with housewives' eczema who are sensitive to rubber gloves need to select gloves based on their skin test results. For the patients who develop immediate allergy in response to latex, caution should be exercised due to possible cross-reaction in response to banana, avocado, kiwi fruit, and melon.[14)]

On the other hand, skin-protective creams designed in consideration of the inconvenience of wearing two different gloves are available, and should be tried. Patients should be instructed to devise daily life plans that are easy on the hands and use the conveniences of modern society. These would include, for example, the use of a dishwasher, sharing of domestic tasks among family members, eating out and utilization of fast food. When going out in winter, gloves should be worn for protection against low temperatures.

The market is flooded with many non-prescription moisture-retentive agents. These agents use mixtures of different ingredients to achieve moisture-retention. Commercial products containing urea have recently appeared,

and these provide a long-lasting moisture-retentive effect and appear to be superior to similar products prescribed in hospitals.[15] These products' moisture-retentive effect can persist for as long as 2 weeks, even after discontinuation of use, and by themselves they can restore the barrier function of the stratum corneum.

With respect to allergens, there is concern that the new European coins in use beginning this year may cause nickel allergy, depending on the alloy used. Recent experiments suggest the possibility that nickel leaches from these coins and invades the skin of the palms when the coins are grasped strongly for as little as 2 minutes.[16] Patients with housewives' eczema should be alert to such possibilities.

The recent boom in nail art has made nail shops common in Japan. Attention should be given to the delipidization of the fingertips caused by polish removers containing toluene and other organic solvents.

Wearing cotton gloves is recommended when touching newspapers and magazines. Although environmentally friendly pulps have recently been manufactured, some literature suggests that there is a risk that these pulps contain sensitizers such as oxides of the resin called rhodine, unlike conventional chemical pulps.[17] This example indicates that environmentally friendly goods are not necessarily human-friendly.

Conclusion

I conclude that housewives' hand eczema is typically a lifestyle-related skin disease. Irrespective of any predisposition, its development and exacerbation depend on a patient's awareness of causative and preventative factors. As women are increasingly assimilated into society beyond the household, the proportion of women with housewives' eczema may become lower than that of men presenting with this eczema. Clinicians should continue to pay attention to changes in society and the environment and should include daily life education in patient interviews.

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