

# AMDD Vol.8

## NEWSLETTER

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\*English translation of Japanese newsletter

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### Improving the Quality of Leukemia Treatment and the Possibility of Radical Treatment

*Patients with leukemia—once an “untreatable disease”—are now expected to achieve complete remission or even be fully cured. We spoke to Dr. Shinichiro Okamoto, Professor in the Division of Hematology, Department of Internal Medicine, at Keio University School of Medicine, to find out more.*

#### **Development of an amazing “molecular-targeted medication”**

Chronic myelogenous leukemia (CML) is a disease where cancerous hematopoietic stem cells in the bone marrow cause uncontrolled proliferation of white blood cells. In the initial chronic phase, white blood cells at various stages of maturity increase and the disease progresses slowly. However, after three to four years, the disease evolves into an acute blast crisis (the manifestations of which are similar to those of acute leukemia), when only immature cells (blasts) increase. Previously, the only way of treating chronic phase CML was to use “anti-cancer drugs” to control the number of white blood cells, although many patients died from an acute blast crisis three to four years later. A breakthrough came with “molecular-targeted medication,” and in 2001, the highly effective drug Imatinib (marketed as Gleevec) appeared on the market. Today, around 93% of patients survive for at least ten years.

#### **Lodging of donor hematopoietic stem cells in the bone marrow**

Since bone marrow transplants began in the 1970s, the frequency of hematopoietic stem cell transplantation has increased year by year. In Japan, around 2,000 transplants using various hematopoietic stem cell sources—such as bone marrow, peripheral blood and umbilical cord blood—are performed each year. With the exception of CML, for which molecular targeted therapy has become the preferred treatment of choice, many

hematopoietic tumors are still treated mainly through hematopoietic stem cell transplantation.

In cases where hematopoietic stem cell transplantation is performed, all the healthy cells left in the bone marrow and the blood are destroyed along with the leukemia cells through strong anti-cancer drugs and radiation prior to transplantation. The healthy hematopoietic stem cells collected from the donor are then transfused into the patient in the same way as a blood transfusion. Eventually, the donor hematopoietic stem cells are engrafted within the patient's bone marrow, starting the production of healthy blood cells. However, hematopoietic stem cell transplantation has major limitations. Not only must a donor have the matching human leukocyte antigen (HLA) type of the patient, but the patient must also be comparatively young and able to withstand transplantation, since rejection and infection also pose problems. Recently, however, transplantation techniques have become more advanced, and transplantation is now readily performed in elderly patients as well.

**In the case of peripheral blood stem cell transplantation, regular apheresis can be used**

Hematopoietic stem cell transplantation through bone marrow transplants is extremely stressful for donors, as it involves harvesting 500~1,000 mL of bone marrow fluid from the donor, under a general anesthetic. However, in the case of peripheral blood stem cell transplantation between blood relatives, which became covered under the Japanese medical insurance system in 2000, donors are administered a granulocyte-colony stimulating factor, which causes proliferation of white blood cells. This results in the manifestation of hematopoietic stem cells in the blood (peripheral blood), which are harvested and transplanted in patients. This method makes bone marrow transplants less stressful for donors compared to those performed in the past and brings many other advantages for patients. For example, the graft is more easily integrated, hematopoietic recovery is quick and the content of hematopoietic stem cells and lymphocytes is higher than that of bone marrow transplants. In October 2010, peripheral blood stem cell transplantation between non-blood relatives was also introduced in Japan, giving both donors and patients greater options. On the other hand, an increase in adverse reactions, such as graft-versus-host disease (GVHD) also gives cause for concern. There seems to be steady progress being made in the development of medication and devices (ECP, etc.) to alleviate such GVHD, but since drugs and devices available in Europe and America are not immediately available in Japan, there is now a pressing need for the issue to be resolved as soon as possible.

Once considered extremely difficult in the past, hematopoietic stem cell transplantation, has now become the standard treatment thanks to various evaluations, studies and safety checks. Although problems still remain, these advances have opened up further possibilities for transplantation therapy. In the future, radical treatment of leukemia is expected through therapies such as treatment with molecular-targeted medication, hematopoietic stem cell transplantation and chemotherapy combined with more effective pre-treatment procedures on patients.

\* This is a summary of the interview with Dr. Okamoto, edited by the editorial desk.

Dr. Shinichiro Okamoto  
Keio University Hospital Professor, Department of Internal Medicine  
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of Medicine

Dr. Okamoto graduated from Keio University School of Medicine in 1979 and subsequently finished his master's degree at Keio University Graduate School of Medicine. In 1985, he began his research at Emory University and the Fred Hutchinson Cancer Research Center in the United States. In 1990, he was appointed a research assistant at The Institute of Medical Science, Tokyo University, and led the Internal Medicine Bone Marrow Transplantation Team. Dr. Okamoto assumed his current position in 2009, after serving as a full-time professor and an associate professor at Keio University and as MD of the Division of Hematology and Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine.

## **Promotion of Medical Innovation and Development of the Medical Devices Industry**

By Mr. Koji Hachiyama

Counselor for Policy Planning Coordination, Cabinet Office's Medical Innovation Promotion Office

It has been said that sooner or later, Japan will no longer be able to function unless it puts common sense aside and makes fundamental reforms based on completely fresh ideas across all sectors, not just in medical care. In the wake of the Great East Japan Earthquake, I believe people in Japan are once again acutely feeling the need for reform. The medical innovation initiative is a move to fundamentally review the nature of medical care in Japan and develop the medical care sector into a true industry for growth. I would like to explain this initiative.

### **Positioning of Medical Innovation in the New Growth Strategy and the Government's Promotional Structure**

The "life innovation" growth strategy for the medical care, health-related and nursing care industries is a key element of Japan's New Growth Strategy formulated by the government last year. The life innovation strategy clearly positions the medical care, nursing care and health-related industries as industries that will drive Japan's growth in the future. The government has set a target of creating a new "life innovation" market worth 45 trillion yen by the year 2020, which will in turn generate 2.8 million new jobs. One particular focus of the life innovation strategy is the promotion of medical innovation (the practical application of cutting-edge medical technology in fields such as pharmaceuticals, medical devices and regenerative medicine). The Medical Innovation Council, chaired by the Chief Cabinet Secretary, has been set up for the purpose of developing globally competitive medical care-related industries, and translating the achievements of these industries into improvements for the medical care and health of the Japanese people. In addition, the Medical Innovation Promotion Office has also been set up in the Cabinet Office to act as the "government's control tower" in promoting medical innovation.

### **Targets for Medical Innovation**

As Japan's population continues to age, the medical care system is required to meet more sophisticated and diverse needs than ever before. Under such conditions, the government plans to provide the Japanese people with medical care that is very cost-effective and among the best in the world by promoting medical innovation. Through medical innovation, diseases that were previously unmanageable can be overcome: illnesses can be prevented and symptoms can be stopped from getting worse, enabling people to live long and healthy lives; the nursing care workload can be alleviated by reducing the number of

people requiring nursing care; unnecessary medical expenses can be pared through the prevention of adverse drug reactions; and medical expenses can be used effectively based on predicted efficacy. As such, the government further intends to develop the medical care sector into a new growth industry that will drive Japan's future economic development, through the active development of pharmaceuticals and medical devices originating from Japan, and their dissemination to the rest of the world.

To these ends, the government is examining the following basic principles. (1) Pool the nation's wisdom and take full advantage of Japan's strengths to practically apply technologies that are globally marketable, (2) Aim for fundamental system reforms, while simultaneously notching up successes in the short-term, (3) Eliminate industry, university and government red tape and make bold budget allocations and regulatory reforms in strategic areas, and (4) Build a new forward-looking medical care system combining Great East Japan Earthquake recovery plans and medical innovation.

### **Specific Initiatives in the Medical Devices Sector**

If the medical devices industry is to further develop, more of the “manufacturing” companies that are Japan's strength must enter the medical devices market, building a strong industrial structure. In particular, it is essential that SMEs with high levels of technical expertise enter the medical devices market. To ensure this, the government must support the creation of programs, infrastructure and networks that facilitate entry by companies from different sectors and further invigorate the medical devices market.

Medical devices produced in Japan must also contribute to global health. To achieve this, we must create an environment conducive to research and business that will attract many research groups to Japan from around the world. We must also consider a standardization strategy for disseminating technologies overseas. We must formulate a strategy for marketing medical care systems in the form of a package that includes the medical device/technique with training. This inevitably requires close collaboration with overseas agencies.

Moreover, future use of medical devices in areas not covered under the health insurance system, such as public health and immunization, is expected to become more widespread. Also, due to advances in regenerative medicine and personalized medicine, which are expected to revolutionize health care in the future, the expectations of medical devices will likely change in the future. We should perhaps anticipate these changes in the healthcare system over the medium-to-long term and focus on developing medical devices that will be in demand globally in the future.

In the meantime, it is also important to examine ways to mitigate the risks involved in developing innovative medical devices. Along with the necessary legislation, it will also be vital to gain public understanding for our position on the risks and the benefits. This will require steady efforts to continue disseminating accurate information and dealing properly with harmful rumors.

Through these initiatives, we aim to turn Japan's medical devices sector into a globally competitive industry.

### **Conclusion**

The importance of innovation in the medical care sector has been brought up many times

in the past, but has been difficult to achieve due to red tape. However, the Japanese government has finally set up a Medical Innovation Promotion Office in the cabinet office and launched a full-scale initiative. With the industrialization of the medical industry harboring enormous potential, the challenge for us in moving forward will be how we can break down existing barriers, and in how far the industry, universities and the government are willing to go to demonstrate their commitment to Japan's future. I fervently hope that we will all unite in building a new future for Japan.

Mr. Hachiyama joined METI in 1992. After serving in METI's Asia and Pacific Division and Bio-Industry Division, he was involved in the administrative reform of medical care, nursing care and pension systems as a member of the Office for Promotion of Reform of the Ministry of Health, Labor and Welfare, a reform team established by and directly under the control of then MHLW Minister.

He returned to METI in 2009, where he continued to focus on the industrialization of the pharmaceuticals and medical devices sectors as Counselor for Policy Planning Coordination for new bio-related businesses. He assumed his current position in January 2011.

## **Patient's Voice**

### **Advanced Medical Care Should Be Delivered Immediately to Those Who Need It**

By Ms. Akiko Hashimoto

Chief Director, NPO Blood Disorder Information & Support Service "Tsubasa"

Permanent Member, The Japan Marrow Donor Program

Senior Counselor, The Cancer Telephone Information Service

Representative, "Tsubasa" Support Fund

It was in 1987 that I first heard a doctor tell me, "If there was a program like the National Marrow Donor Program (NMDP) in Japan, your son's illness could be cured." At the time, my son was ten years old, suffering from chronic myelogenous leukemia (CML), and we had just discovered that his HLA type did not match that of his sister—his only sibling. Back then, a bone marrow transplant was the only way to treat this disease, so a donor was essential. At the time, the National Marrow Donor Program had just been established in the United States, but Japan offered no such program.

I immediately appealed to the MHLW, the Diet and the media, going around Japan explaining that Japan also needed to have a marrow donor program. Before long, the campaign for a nationwide bone marrow bank system began to get noticed across Japan and 770,000 petition signatures were collected, which compelled the Diet to act.

However, in December 1991, just three months after the news that the Japan Marrow Donor Program had been established and begun operations, my son passed away. It was too late.

Since then, I have continued to support patients in the field of blood disorders and childhood cancers, but the one notion that is permanently etched in my mind is that "advanced medical care should be delivered immediately to those who need it."

In 2001, molecular-targeted medication, which is amazingly effective in treating CML, was developed. Since then, more than 90% of patients remain in remission, leading normal healthy lives. However, the multiplier effect of the deterioration of the Japanese economy

on an already expensive drug led to a situation whereby some people could not afford a drug designed to treat their individual condition. As such, besides submitting a proposal asking for a government review of high medical care expenses in 2009, I set up the Tsubasa Support Fund in 2010. The founding concept was the same: “Any effective medical treatment that is out there should be made available to all those who need it.”

The Cancer Telephone Information Service also began to receive an increasing number of distressed calls from people, saying things like, “I’m glad I was cured by my transplant, but I still suffer from pins and needles three years on,” “After treatment with anti-cancer drugs, I’ve been left with a taste disorder,” or “After my transplant, I lost the use of my legs.” However, from a different perspective, the increase in the number of calls made directly by patients themselves is also indicative of improvement in treatment outcomes.

In this context, during a lecture organized by The Japan Society for Hematopoietic Cell Transplantation this spring, I heard a report of a medical device developed in the United States that could alleviate disorders commonly occurring after a bone marrow transplantation. The device, known as ECP, is already being used to treat transplant patients in many advanced countries, which I thought was fantastic news.

The strong will and determination of patients to survive is being met with fervent efforts in the fields of medical care and drug discovery to find a cure. People say that a dream shared by everyone will eventually come true and I think this news allows us to glimpse the dream of “curing patients in a better way.”

## **Medical Journalist Viewpoint**

### **Making Cutting-Edge Medical Technology Readily Available to Patients**

By Ms. Junko Sugimoto

Medical Journalist, Vice Chairman, Medical Journalists Association of Japan

Under Japan’s New Growth Strategy, medical care is positioned as an industry that will drive Japan’s future growth. Given Japan’s current human resource difficulties and financial difficulties, I feel slightly unsure about this.

However, key elements that will no doubt make up for this are technical innovation and government programs. The quality of medical care and Japan’s economy and industry all depend heavily on advanced medical technology. In particular, the ability to provide non-invasive patient-friendly medical care is an imperative of our times, and advanced medical technology is expected to play an increasingly important role in the future.

Medical devices that can support life by accurately and efficiently diagnosing and treating patients have progressed at an amazingly fast pace. However, Japan’s current medical device industry continues to lag behind in the race of global competitiveness.

The size of the world medical devices market is said to be around \$335 billion (more than ¥20 trillion). The United States is the market leader (42%), followed by Europe (34%). Meanwhile, Japan’s market share has remained unchanged for several years (at just 10%) , and its imports exceed exports by ¥500 billion.



Medical devices associations have tried to strike a balance between imports and exports by analyzing why imports exceed exports. Another contributing factor in addition to problems related to healthcare policy was that the majority of therapeutic devices depend on imported components.

Why is it that Japan, which was originally supposed to be a leader in imaging and diagnostic devices with strong exports, is now experiencing slower export growth than emerging economies?

According to those in the know, one of the reasons Japanese manufacturers are reluctant to enter the therapeutic devices market is that it is a national trait to shy away from risk: in other words, Japanese manufacturers do not want to be severely criticized when something goes wrong. And yet, if the Japanese medical devices industry is to survive in the future, Japan must build an industrial structure that allows manufacturers to focus more on the development of advanced medical devices and commercialize newly developed devices as early as possible.

There is no point in developing advanced medical devices unless they are going to be put to practical use to help patients. Talk of introducing advanced medical technology always leads to the problem of tardy approval of medical devices, which has become the normal state of affairs in Japan. The organization set up in 2004, primarily to speed up examination of approval, was the PMDA (Pharmaceuticals and Medical Devices Agency). Efforts to improve the situation appear to have been made, but even today, seven years after the establishment of the PMDA, there has been virtually no improvement. The inefficiency of the interface between the government and manufacturers, and problems with the approval application service, are still often identified. Consequently, manufacturers are forced to obtain licenses in Europe and elsewhere. This problem is hugely detrimental, not only for the industrial sector, but also for society as a whole, since patients are denied the benefits of the advanced medical technology developed expressly for them. A lack of staff with the high level of expertise required for the examination of approval applications is proving to be a major obstacle. Urgent efforts must be made to eliminate the disparity in access to medical devices in Japan, compared to the United States and Europe, through restructuring—including drafting in more human resources with the necessary expertise, and simplifying the examination procedure in certain areas. This will also have an impact on the introduction of new medical devices from overseas and exports to emerging economies.

As such, Japan's top priority must be to establish a system that makes advanced medical technology readily available to the Japanese people and patients. Once this has been achieved, it would be nice if, supported by the growth of medical care related-industries, the medical care industry itself was then revitalized, restoring Japan to its former glory.

## **Report of 19th and 20th Media Lectures**

The American Medical Devices and Diagnostics Manufacturers' Association (AMDD) held the 19th Medical Lecture on February 17, 2011. The theme of the lecture was "Current Status and Issues of Maintenance for Medical Devices."

The first lecture, “Proper Maintenance of Medical Devices,” was delivered from the viewpoint of a radiological technologist, by Dr. Yoshiaki Kitamura, Chairman of The Japan Association of Radiological Technologists and member of the special committee of the Central Social Insurance Medical Council.

Dr. Kitamura talked about the maintenance of medical devices and current activities. The second speaker, Dr. Makoto Kikuchi, Deputy Director of the National Defense Medical College and Professor in the National Defense Medical College Department of Medical Engineering, gave a presentation on current issues revealed by research into the maintenance of medical devices and the legislation of maintenance operations and its present situation. He also explained the preparation of guidelines on the use, maintenance and management of medical devices.

Finally, Dr. Takaaki Kameda, Chairman of the Board of Kameda General Hospital, which operates medical centers around Kamogawa City in Chiba Prefecture, gave a presentation on the safety controls in place at his own hospital, and talked about the benefits of maintenance for medical devices (*please refer to Vol. 7 for details about initiatives at Kameda General Hospital*).

AMDD also held the 20th Media Lecture on July 14, 2011 with the theme of “Cutting-Edge Diagnosis and Treatment of Leukemia.”

Dr. Nobukazu Watanabe, specially-appointed Associate Professor at the Center for Stem Cell Biology and Regenerative Medicine of The Institute of Medical Science, The University of Tokyo, delivered the opening lecture, entitled “Evolution and Outlook of Leukemia Diagnostic Technology.” He explained in detail the necessary procedures prior to bone marrow transplantation and analysis following the transplantation of umbilical cord blood. He also focused on graft failure following the transplantation of hematopoietic stem cells with non-matching HLA, and the features of chimerism analysis/HLA Flow method that are useful for diagnosis of relapse.

Next, Dr. Shinichiro Okamoto, Keio University Hospital Professor, Department of Internal Medicine and MD, Division of Hematology, Department of Internal Medicine, Keio University School of Medicine, gave a lecture entitled “Progress and Issues in the Treatment of Leukemia ~ Expanding Therapeutic Possibilities and Enhancing the Quality of Treatment.” He talked about the emergence of a series of new transplantation techniques for the transplantation of allogeneic hematopoietic stem cells and the future direction in the treatment of leukemia (*please refer to the article “Improving the Quality of Leukemia Treatment and the Possibility of Radical Treatment” on page 1 of this newsletter for a summary of the talk given by Dr. Okamoto*).

## **Value of Medical Technology (Orthopedic Material)**

### **Use of Bone Cement in “Bone Reconstruction”**

For those of you who have trouble conjuring up a mental image of bone cement, it may help if we liken it to dental cement. Bone cement has been used for more than 50 years in



the field of orthopedic surgery, in procedures such as artificial joint replacements. When you hear the word “cement,” you may imagine that bone cement is used like an adhesive, but like dental cement, bone cement acts as a filler, filling in the gaps between the artificial joint and the bone and fixing it in place. Also, another comparatively new use of bone cement is as a treatment for pain caused by vertebra compression fracture from osteoporosis or a bone tumor. Here, the bone cement is injected into the vertebrae through the skin to ease the pain.

Meanwhile, a treatment used in the field of neurosurgery to repair skull defects after brain tumor surgery or depressed fractures is by shaping cement into the shape of the defect. Since brain cement is made by mixing a polymer (powder) and monomer (liquid) in the operating theatre, leading to a reaction in which the cement hardens, surgeons are working against the clock, trying to inject and shape the bone cement at the right time. Besides working on the development of optimal instruments and training programs for the diverse applications of long-term tried-and-trusted bone cement products, manufacturers are also carefully examining the introduction of products available overseas that have not yet been approved in Japan.

(By Asako Hashimoto, Stryker Japan K.K.)

## **Results of “Opinion Survey on Healthcare and Advanced Medical Technology in Japan” Released**

The American Medical Devices and Diagnostics Manufacturers’ Association (AMDD) conducted an internet survey of 2,000 members of the general public and a postal survey of representatives of patient groups to find out how advanced medical technology is perceived by Japanese people and patients, as well as how they would like to see medical devices and the medical care system surrounding medical devices be developed in the future.

The results showed that both the general public (87%) and patient groups (86%) consider “advanced medical technology to be important.” However, results also revealed that patient groups (86%) wanted “access to the world’s latest medical technology” more strongly than the general public (74%), and the percentage of those wanting “access to the world’s latest medical technology” who “want access even if medical fees are higher to some extent” was also higher for patient groups (74%) than for the general public (66%). Also, the percentage who replied that the reason they were dissatisfied with Japanese healthcare was because they could not receive the most advanced medical treatment from overseas was higher for patient groups (53%) than for the general public (35%), showing that many people in patient groups would like to have access to the world’s latest medical technology.

For further details on the results of the survey, please visit the AMDD website (<http://amdd.jp/activities/recommen/index.html>).

### **Value of Medical Technology**

Our mission is to make more people understand the unlimited potential of advanced medical technology and its contribution to the reformation of the Japanese medical care system

\*All opinions in this newsletter are the personal opinions of the authors, and do not necessarily represent the opinions and activities of AMDD.