

Figure 2. Macroscopic evaluation at the end of the 36-week protocol. Rats from group 1 had larger bladder tumors, in clear contrast with rats from group 4.

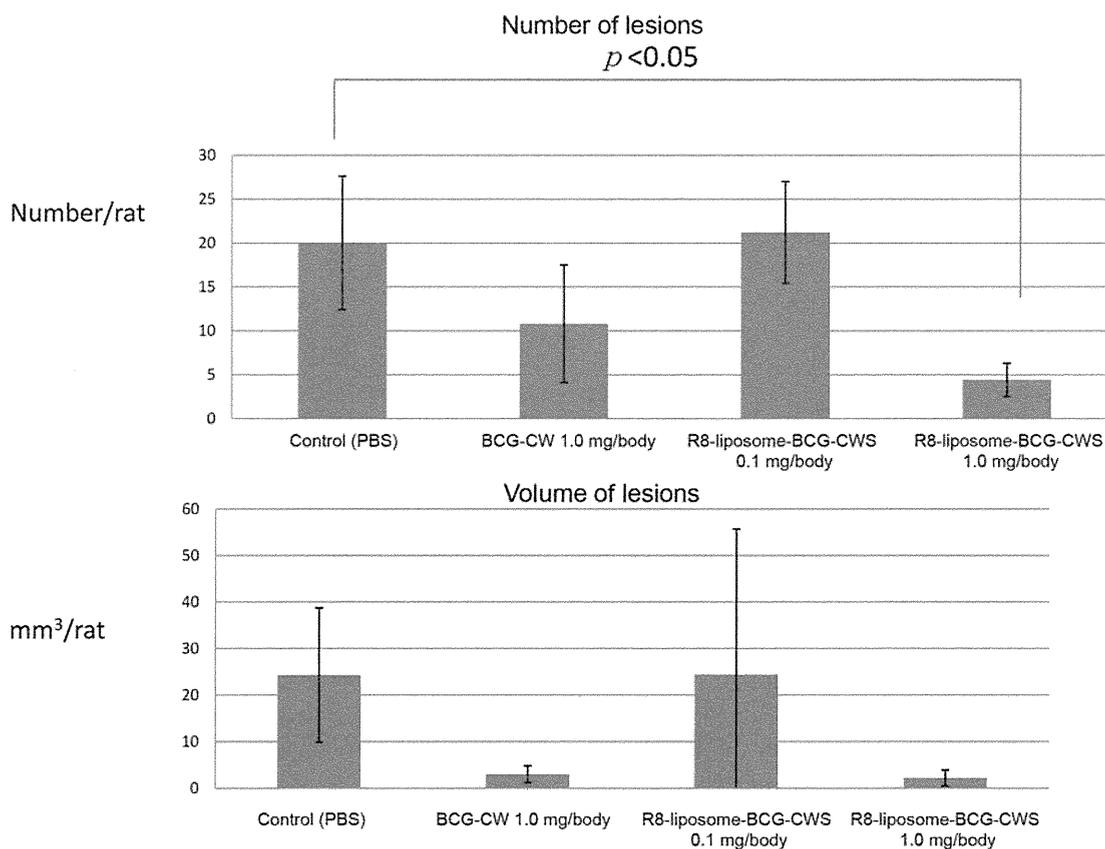


Figure 3. Mean number of tumors and volume of lesions between the four groups. The number of tumors was significantly lower in the group of R8-liposome-BCG-CWS 1.0 mg/body than in the control group, but the volume of tumors was not significantly different between the four groups.

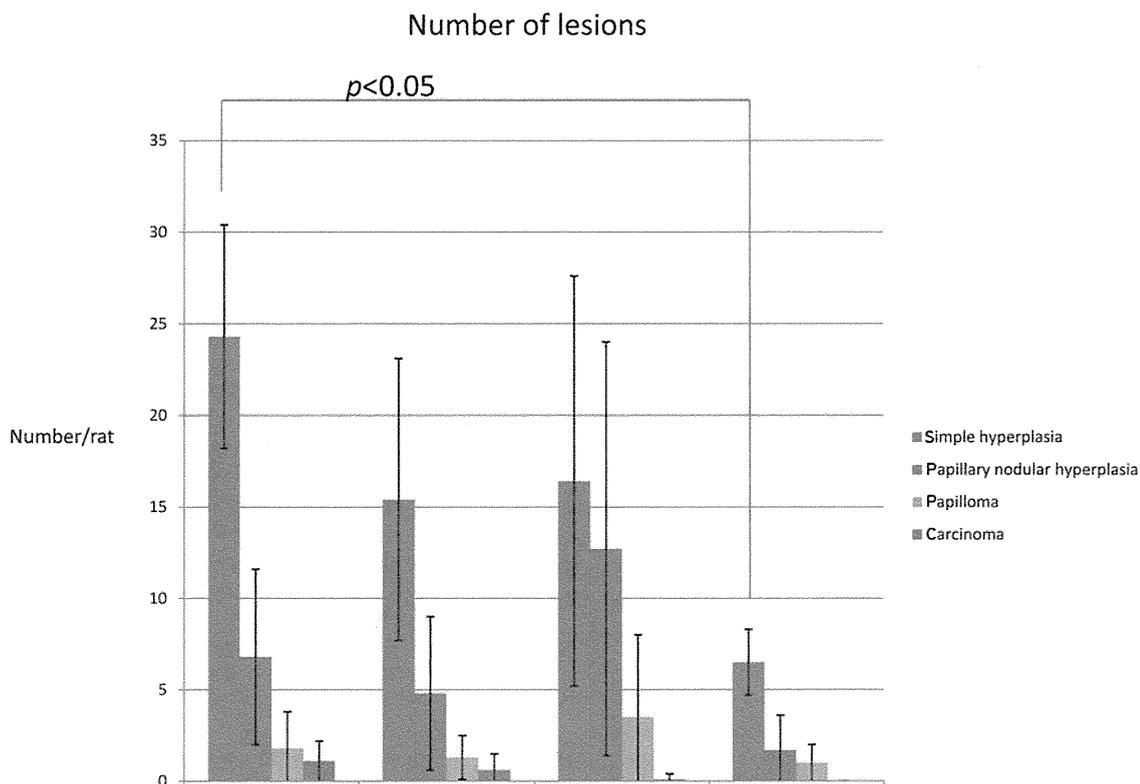


Figure 4. The histological effect of BCG-CW and R8-liposome-BCG-CWS on rat urinary bladder cancer induced. The mean number of simple hyperplasias was significantly lower in the group of R8-liposome-BCG-CWS 1.0 mg/body than in the control group.

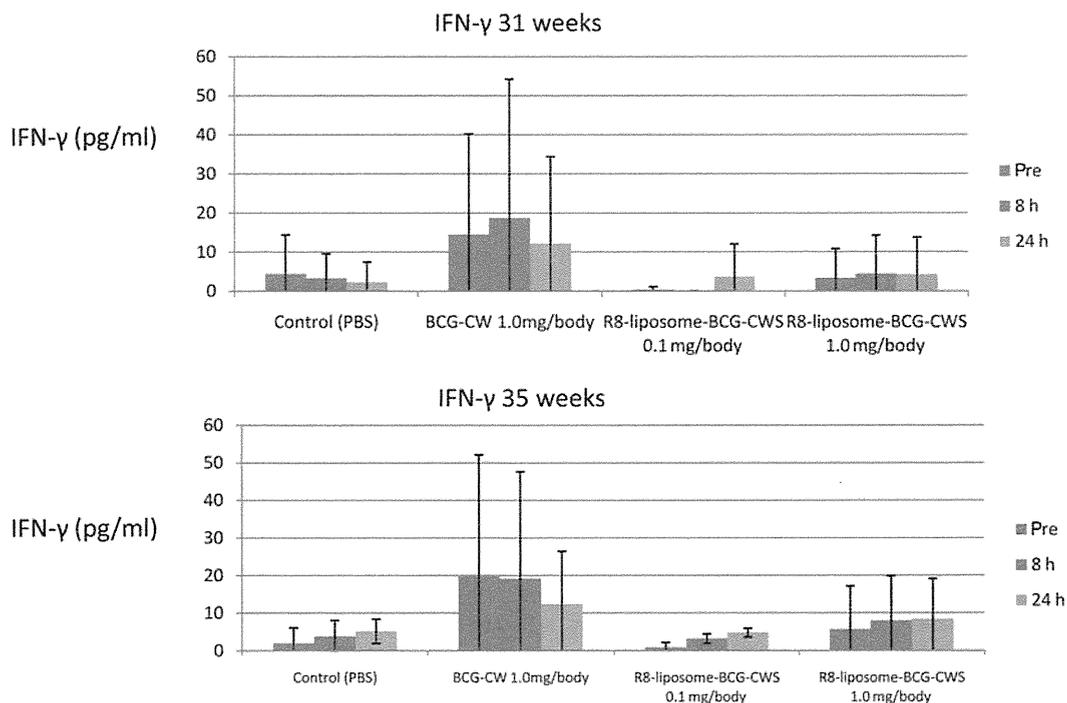


Figure 5. IFN-γ serum level at 31 weeks and 35 weeks. IFN-γ increased remarkably at 35 weeks in the group receiving BCG-CW and R8-liposome-BCG-CWS 1.0 mg/body intravesically.

several possible mechanisms were proposed. In our previous study, induction of surface NKG2D (a powerful activating receptor expressed by natural killer cells) ligands by R8-liposome-BCG-CWS rendered cancer cells more susceptible to cytotoxicity by lymphokine-activated killer cells. T-24 and RT-112 bladder cancer cells, even when cultured singly in the absence of immune cells, can directly respond to R8-liposome-BCG-CWS (12).

IFN- γ has been shown to be important in the function and maturation of multiple immune cells (24). T-Cells, natural killer cells, and natural killer T-cells are the primary producers of IFN- γ which has a myriad of effects in both host defense and immune regulation, including antiviral, antimicrobial, and antitumor activity. IFN- γ also has direct antitumor effects because it is anti-angiogenic, inhibits proliferation, sensitizes tumor cells to apoptosis, up-regulates MHC class I and II expression, and stimulates antitumor immune activity. In a study of recurring superficial transitional bladder carcinoma, it was shown that intravesical instillations of IFN- γ were effective against cancer recurrence (25). Our results are in agreement with the role of IFN- γ production in bladder cancer development and the role of IFN- γ activity in cancer prevention.

In conclusion, when given intravesically, R8-liposome-BCG-CWS significantly inhibited rat bladder carcinogenesis. Development of this non-live bacterial agent may contribute to providing a more active and less toxic tool as a future substitute for live BCG in immunotherapy against non-muscle-invasive bladder cancer.

Acknowledgements

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Meeting Report

The 7th Asia Cancer Forum: From the Perspective of Human Security, How Can We Collaborate as Asians in Order to Place Cancer on the Global Health Agenda? How Can We Fill in the Gaps that Exist Among Us?

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This forum has continued to discuss the inclusion of cancer on the global health agenda, and specifically the Millennium Development Goals. The seventh forum presented an overview of activities to date, supplemented by reports from Korea, local governments in Japan and representatives from the pharmaceutical industry. Discussion focused on how to engage in measures to tackle cancer prevention and achieve early detection and effective treatment, using limited resources. It was recognized that with non-communicable diseases gaining increasing attention in international dialogue, it is now of the utmost importance to share an accurate recognition of cancer research and treatment throughout Asia and the wider world. Participants concurred that cancer issues are decoupled from the development aid agenda and that cooperation should be advanced on the basis of international cooperation without recourse to governmental development aid.

Key words: technology gaps – information sharing – MDGs – maximizing resources

OVERVIEW

The Asia Cancer Forum is a grouping that aims to discuss cancer science and policy issues among Asian countries. The basic concept of the forum is that discussion will enhance sharing and awareness of the issues and each of the

participants will gain their own take home message to apply to their own activities as the outcomes of the forum. The forum is operated through the research funds of the participating members and receives support in the form of Health and Labour Sciences Research Grants from the Ministry of

Health, Labour and Welfare of Japan, as part of the Third Term Comprehensive Control Research for Cancer or its ongoing work to create an Asian network. The organizer of the forum is N.K. and it is chaired by H.A., both of the Research Center for Advanced Science and Technology (RCAST), the University of Tokyo.

The origins of the Asia Cancer Forum date back to 2004 when a group of Asian researchers launched a platform called the Asia High Technology Network to discuss issues in the field of medicine. The grouping engaged in discussions on the formation of an Asia Cancer Information Network. From 2008, the name of the research platform was changed to the Asia Cancer Forum and the first two meetings were held thereafter. The third meeting was held in February 2009, on the theme of 'Health, Information and Development'. The third meeting was held jointly with SciDev.Net and saw discussion focus closely on issues relating to the setting of the global health agenda. The fourth meeting was held in April 2009 under the theme of 'Asian Challenges in Shifting the Disease Burdens'. In November 2009, the fifth meeting was held in collaboration with the 20th Asia Pacific Cancer Conference (APCC) under the theme of 'What Should we do to Raise Awareness on the Issue of Cancer in the Global Health Agenda?' The meetings, to date, have concentrated on ways to share information among Asian research colleagues, thus raising awareness of the importance of including cancer on the global health agenda.

In the Sixth Asia Cancer Forum, discussion had focused on the difficulties in achieving a comprehensive cancer information network in Asia, due to technology and know-how gaps between frontrunner countries and developing countries. These discussions led to the theme of the Seventh Asia Cancer Forum being set as 'From the perspective of human security, how can we collaborate as Asians in order to place cancer on the global health agenda? How can we fill in the gaps that exist among us?'

The Seventh Asia Cancer Forum was held at the University of Tokyo, Japan, on 3 November 2010. The meeting consisted of two sessions consisting of six special presentations, followed by detailed discussions. Approximately 20 people were present and the meeting provided a forum for active discussions. H.A. [Research Center for Advanced Science and Technology (RCAST), the University of Tokyo] presided, with organization being implemented by N.K. (RCAST).

PRESENTATION 1: SETTING THE ISSUES: DISCUSSION POINTS AND CHALLENGES FOR THE ASIA CANCER FORUM TO DATE

N.K. (RCAST) noted that with regard to the discussion points and challenges raised by the Asia Cancer Forum to date, the primary challenge has been that cancer has yet to be included in the Millennium Development Goals (MDGs). It is extremely important for specialists to have a common

understanding of the issue of raising cancer on the global health agenda. At the time of the 5th Asia Cancer Forum, participants discussed the importance of cancer being included in the MDGs. This has recently become an important issue globally. Surveys have been implemented on awareness of cancer as a global health issue. There seems to be an awareness gap among cancer specialists about the importance of including cancer on the global health agenda. The WHO will be taking up non-communicable diseases (NCDs) as part of its efforts, with the holding of a UN General Assembly Summit on NCDs in September 2011.

With regard to the implications of the awareness gap concerning challenges being faced, it is important to recognize that we are no longer in an aid-based world. Cooperation and collaboration must be ensured in an equitable manner as partners. It is necessary to gain the broad participation of cancer researchers in order to decipher the current challenges in industrialized nations.

With regard to future themes for consideration, it is important to transcend existing frameworks and take a multidisciplinary approach with the aim of getting as many people as possible to understand the situation. It is also important to search for ways in which Japan, China and Korea can cooperate, focusing on relations with middle-income emerging economies. In the development of cancer prevention, diagnosis, treatment and care, we need to remind ourselves of stratified strategies for different situations. To date, especially in Japan, the prevailing concept is that patients must be cured, whatever costs may be incurred. It is very important to bear in mind resource limitations in various countries, however, and tailor responses to match budgetary realities.

H.A. (RCAST) thanked N.K. for her overview to the activities of the Asia Cancer Forum.

PRESENTATION 2: THE RAPID CHANGING PATTERNS OF CANCER IN KOREA DURING THE LAST THREE DECADES WITH SOME SUGGESTIONS FOR CANCER PREVENTION

EARLY DETECTION AND TRANSLATIONAL RESEARCHES FOR NOVEL THERAPY AS A MEDICAL ONCOLOGIST'S VIEW POINT

J.K.R. (Yonsei University College of Medicine) provided Korean data about the changing patterns of cancer and what they mean for cancer control. Cancer has been the most common cause of death in Korea since 1983. Cancer incidence is now 250 per 100 000 population. Korea has achieved dramatic economic development during the last several decades. Cancer incidence is increasing rapidly and the prevalence rate is changing variously. The cancer survival rate has improved considerably during the last two decades.

Korea has industrialized during the last several decades, and until relatively recently, most people lived in rural areas. However, most people now live in urban areas. Seventy to

80% of Korean people live in apartments and enjoy improved standards of hygiene. Diet has become increasingly westernized, moving to high calorie, high fat and lower fiber foods. Koreans have a dynamic and positive attitude for novel therapies and new drugs.

In 1960, the annual income of Korea was \$100 per capita. In 2009, that had increased to US\$25 000. Mandatory national health insurance has achieved almost 100% coverage of the population and complete check-ups are provided as standard. There is a national cancer screening program and voluntary check-ups for early detection. In addition, there is aggressive competition between five mega hospitals in cancer treatment.

In 1983, cancer became the most common cause of death in Korea and has increased since then, being the cause of death for 27% of all deaths. Korea's population is now almost 50 million, representing 0.76% of the global population, but accounts for 1.31% of all cancers around the world. Prostate cancer is increasing in males. In females, cervical cancer used to be the most common form of cancer, but this has since been surpassed by other types, including breast and thyroid cancer. The number of expected new cancer cases is also increasing. In men, the incidence of stomach cancer is decreasing, but colorectal cancer is increasing dramatically. In women, the most dramatic increase has been in breast cancer. The 5-year survival rate has also seen marked improvements.

The number of cancer patients is increasing by about 8% annually. Patterns of cancer prevalence have been changing rapidly during the last two decades. Survival has increased over the last two decades due to: (i) primary prevention, including an anti-smoking campaign, (ii) a national screening program for early detection and (iii) improvement of treatment modalities, including multidisciplinary and multimodality approaches.

In the western world, the cure rate for cancer stands at about 60% due to improved diagnosis and treatment modalities. This is thanks to surgery, radiotherapy and chemotherapy. The issues are as follows: (i) How to prevent tumorigenesis? (ii) How to improve early detection? (iii) How to predict and detect recurrences and metastasis? (iv) How to predict the tumor response or resistance? (v) How to predict therapy-related toxicities? To solve these problems, genome-wide research and data are required.

Yonsei University was the first westernized hospital in Korea and since its establishment in 1884 has continued to develop. The Cancer Center was established in 1969. In order to understand tumors, a tumor registry and tumor bank were created 15 years ago. There is also a computerized follow-up system. The data bank now contains a total of 95 166 cases and this number continues to grow year by year. In terms of tumor registration trends in recent years, the number of thyroid cancer cases has recently increased. Yonsei University Hospital is treating ~5% of all cancer patients in Korea. Five-year survival rates are particularly good for stomach cancer and 5-year survival rates have increased

overall. Yonsei University Hospital has an equivalent or superior cure and survival rate compared with western countries. However, there are still few novel therapeutic techniques and few novel anti-cancer drugs. There is a further need for world-class research and global collaboration.

In terms of clinical trials and translational research, good clinical practice (GCP) guidelines were created in the 1990s in Korea. International GCP guidelines were adopted in 2001. There are a number of centers and trial groups implementing clinical trials. Yonsei University has international collaborations with various institutions, including the Mayo Clinic and the University of Rochester and others in Europe and Latin America. It is also a member of OncoNet, which includes preeminent cancer-related institutions around the world. Efforts are also concentrating on personalized therapy, focusing on accurate diagnosis and tumor staging, proper evaluation of host status and selective tumor kill with minimal damage to normal tissues. In addition, the personalized method helps in the selection of patients for target drugs. Cancer requires a genome-wide approach, incorporating tumor heterogeneity, multistep processes and complex intracellular processes, and also confirmative clinical trials.

In order to overcome the current status and to cure cancer, primary prevention is most important. Smoking cessation is most important, particularly in Japan, China and Korea, especially with regard to passive smoking. Early detection is also essential, including national cancer screening programs and novel universal tumor markers. There is a need also to bridge the difference between the bench and the bed, which requires translational research and collaboration between basic, translational and clinical researchers. Cooperation between Asia-Pacific countries is essential for future progress to be achieved.

PRESENTATION 3: BASED ON DISCUSSIONS AT THE 6TH ASIA CANCER FORUM (SHENZHEN, CHINA), WHAT DOES THE GAP BETWEEN THE CURRENT STATUS OF CANCER RESEARCH AND TREATMENT IN JAPAN, A FRONTRUNNER IN THE FIELD, AND THE PERCEPTION OF ISSUES IN DEVELOPING COUNTRIES MEAN FOR FUTURE ACTIONS?

H.A. (RCAST) posed the question as to why there has been no recent advancement in cancer research in Japan. It could be that Japan is preparing for the next big leap. If Korea's situation matures, it is possible that Korea could face the issues that Japan is currently facing. The situation in high-income countries could be presented to middle-income countries as examples of what it is good to do and what should not be done.

The *Japanese Journal of Clinical Oncology*, v.40, supplement 1, 2010, includes a summary of discussions held at the working groups at the 20th Asia Pacific Cancer

Conference (APCC). Through these discussions, it was recognized that cancer must be a global health agenda item and that the Asia-Pacific is ready to start towards this goal. The purpose of the Asia Cancer Forum is to share knowledge and experience between Japan, China and Korea.

In Asia, the population is rapidly growing and there is a rapid migration of age distribution towards a greater proportion of aged population as longevity increases. There has also been an increase in quality of diagnosis and treatment and an increase in new drug development. There are disparities in economic development among the countries of Asia, which presents challenges for the future.

In Japan, the population demographic and disease structure have rapidly changed. The cost of medical care is also rapidly increasing and the pharmaceutical market is expanding. In Japan, there is a particular problem with drug lag, which is generally twice as long as the drug lag in the USA.

In order to develop new treatments, it is important to have large-scale clinical trials, but this cannot be implemented by Japan alone. It is important to recognize the ethnic differences between Asians and western populations and work together with China and Korea on therapies and treatment that are best suited for Asian people. Japan is engaged in international clinical trials, together with China and Korea. 'Expansion of cancer care and control in countries of low and middle income: a call to action' is a recent article in the *Lancet*, which advocates activities similar to what the Asia Cancer Forum is aiming to achieve.

Substantial inequalities exist in cancer survival rates across countries. In 2009, the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries was established.

With regard to what can be done by academia, we need to improve medical education and the distribution of medical care. We need to improve access to clinical trials and manage these trials effectively. We need also to make concerted efforts to collect information from clinical trials.

The Asia Cancer Forum examines means for sharing information in a meaningful and comparable manner. To establish an information technology network for opening up cancer issues for global health consideration will be an important approach. It is reasonable to collaborate with policy-makers in government and from the private sector, including pharmaceutical companies. Post-marketing surveillance, which is ongoing in Japan, is an example to establish tailor-made uses for drugs and treatments that are best suited to patients. Such information will be useful not only for Japanese but also for other Asian patients belonging to a similar ethnicity.

PRESENTATION 4: CANCER AS A NEW GLOBAL HEALTH AGENDA

H.I. (Department of Health and Welfare, Chiba Prefecture) explained that in recent years, health experts have come together to highlight the global nature of cancer issues.

With regard to the worldwide trends in cancer, it is noticeable that cancer prevalence is increasing and it is expected that cancer will continue to be the leading cause of death in the world, along with ischemic heart disease and stroke. Cancer used to be a disease isolated to developed countries, but today, the situation has changed and most cancer cases are now found in developing countries and that the ratio is going to increase. In terms of the ratio of mortality to incidence in 1 year, the mortality is highest in low-income countries and lowest in high-income countries. There is a disequilibrium in cancer whereby the disease burden caused by cancer is very great in developing countries, but global resources for cancer are concentrated in the developed countries.

In recent years, cancer has gained increasing attention in the international community. Concerning cancer in developing countries, the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries (GTF.CCC) was established in 2009. A UN General Assembly Summit on NCDs will be held in 2011. In comparison, relating to mother and child health, UNAIDS was established in 1996, which was followed by the MDGs in 2000 and the establishment of a global fund in 2002. It is encouraging that a similar movement is now happening with cancer. Following the creation of the MDGs and the global fund in 2002, there was a great improvement in access to funding and it is to be hoped that a similar trend will be seen with cancer. However, the countries mainly affected by NCDs are not low-income countries, but middle-income countries, and therefore, it is unlikely that similar funding will be made available for cancer. Cancer is decoupled from poverty issues and this fact could impede efforts to gain further funding for a global fight against cancer.

The epicenter of cancer is in Asia, with approximately half of all deaths from cancer being located here. Japan boasts the lowest mortality rate for the three major diseases among the G7 countries. Japan is facing the issue of cancer head-on compared with other nations and is also facing a rapidly aging society. The expectations for the Asia Cancer Forum are to promote an accurate recognition of the realities of cancer and the global health agenda for cancer. It should be recognized that Asia is at the epicenter of cancer and that non-governmental players should increase their involvement. With limited resources, it is important to create a structure for combating cancer under financial restrictions, as it is likely that funding will become increasingly tight in future years.

T.T. (Institute of Gerontology, The University of Tokyo) noted that cancer is a disease that will probably be left until the very end of the global agenda. Japan is experiencing an unprecedented aging of the population, which presents issues not merely about growing old, but also about quality of life. Quality of life is closely related to quality of medical care. From that perspective, the prolongation of life is very important for cancer treatment. Different kinds of care including palliative care are very important. Korea, China and Taiwan are also experiencing aging of their populations. Recently, a

meeting of specialists from Asia shared the same awareness of the aging issue and how our economies should respond to the problem. Economic development in Asia comes hand in hand with the problem of aging in Asia. The issue of cancer is not just about developmental assistance, and knowledge held by non-governmental agencies will also be vital.

PRESENTATION 5: CANCER CONTROL: LESSONS FROM GLOBAL HEALTH INITIATIVES

K.S. (Graduate School of Medicine and Faculty of Medicine, The University of Tokyo) noted that although the global health community is accelerating its efforts to achieve the health-related MDGs, there is a growing momentum to push NCDs, including cancer, onto the global health agenda, notably at the UN General Assembly summit in September 2011.

There are several myths about cancer in developing countries. A common perception is that cancer is not everybody's problem but a disease of affluence and of the elderly. Another common notion is that the provision of cancer treatment and prevention is not feasible and too expensive in low-resource settings. Such perceptions are clearly wrong.

One of the greatest challenges confronting the global health community working toward the MDGs has been the fight against HIV/AIDS. A decade ago, critics who argued against the feasibility of anti-retroviral (ARV) treatment with second-line drugs asserted that complex care could not be scaled up within weak health-care systems. This was proven to be wrong given the enormous success of the ARV roll-out. The question is whether it is possible to apply the analogy to cancer control in middle- and low-income countries.

The global cancer community, including the Asia Cancer Forum, needs to consider at least three things to make this happen as regards cancer control. First, there has to be a demonstration of results through the development and implementation of a cost-effective delivery strategy, which requires a paradigm shift away from an emphasis on scientific discovery to the implementation and evaluation of a package of preventive and curative interventions. Second, a multiple-stakeholder approach is needed, including policy-makers and pharmaceutical companies for global and regional drug pricing and procurement mechanisms. Finally, the development of an innovative mechanism for both external and domestic financing in developing countries is also required. All of these innovations are a real challenge and a central theme of the current global movement toward universal coverage.

Next year, Japan will celebrate the 50th anniversary of its universal health insurance coverage. According to Horton,¹ Japan is 'a mirror of our future'. It seems that Japan is in a comparatively good position to take the lead and help set the future global health agenda (e.g. post-MDGs). However, the

discrepancy between the financial commitment and public/political support means that there is a system failure in terms of reflecting public views on policy.

The fundamental problem of modern Japan is the lack of connectedness. First, the fragmented nature of relations between the different ministries and agencies within Japan prevents any form of coordination between foreign and national health policies. Experts in global health are also detached from those working in the field of national health, when they should be working together. Second, Japan has expertise within its own borders, but this is seldom transferred to the global health arena. Finally, a robust scientific assessment of Japan's national and foreign health policy has been lacking, and therefore, lessons and knowledge about best practice are not transferred effectively. The *Lancet* series on Japan is perhaps the first opportunity we have had to discuss and evaluate Japan's national and international health policy in a scientific manner.

The concept of global health will help to identify the need for restructuring domestic health policies and systems, which in turn will reinvigorate Japanese domestic and global health strategies including cancer control.

PRESENTATION 6: DEVELOPMENT AND DELIVERY OF ANTI-CANCER AGENTS IN ASIAN COUNTRIES

M.I. (GlaxoSmithKline K.K.) explained that the current situation for pharmaceutical companies is that R&D funding and drug approvals are decreasing. There is a need to identify the real clinical benefits and long-term safety. In order to do this, it is necessary to conduct a large-scale study and recruit sufficient patients internationally. There is a need to prepare large investment. Multiregional clinical trials (MRCT) are increasing in Japan and are needed as Japan alone is unable to implement large-scale trials. Korea is an active promoter of MRCT and both Taiwan and China are moving toward increased numbers of clinical trials.

Research is also required for the individual differences in drug response. One example of this is progression-free survival in epidermal growth factor receptor (EGFR) mutation-positive and -negative patients for which the effects of gefitinib were investigated. This drug proved to be very effective in Asia and it was therefore deemed to implement another MRCT trial called 'IPASS'. This IPASS demonstrated that gefitinib was effective in treating EGFR mutation-positive patients, which includes many Asian people.

Safety is another aspect that needs to be focused on. In the case of sunitinib, for renal cell cancer, the Japan study showed considerably elevated figures over those gained from foreign trials. This demonstrates that safety concerns can vary from region to region.

In terms of opportunities for Asia collaboration, the similar ethnic, dietary and social habits of people in Asia are good for joint efforts. The global pharmaceutical market is

continuing to grow, although the percentage of the market accounted for by the USA has decreased slightly. The pharmaceutical markets in emerging economies are growing rapidly and the forecast is that the Asian countries will continue to grow. Several anti-cancer agents have already developed through collaboration in Asia, and Asian contribution to new drug launches is now very clear. Looking at the delivery of those newly developed agents, however, it is recognized that there could be high hurdles for their smooth delivery to patients, mainly due to the high drug price and the limited reimbursement process in each insurance system. International consideration to overcome them and deliver new drugs for all patients appropriately will be an urgent matter, in order to achieve a good balance between the supply of the resources at the development phase and the delivery of the approved anti-cancer drugs after launch, and to keep equalities across countries in this region. The pharma-industry has to develop several measures to tackle this need from the society.

DISCUSSION

M.N. (Medical Platform Asia) noted that it is necessary to identify what steps to take on achieving the inclusion of cancer on the global health agenda. He stated that he has great expectations for the Asia Cancer Forum to grow.

A.N. (Chiba Cancer Center) noted that listening to the presentations and viewing the reality on the frontlines of cancer are very exciting. There is a move to personalize and equalize treatment in Japan and each prefectural cancer center plays a significant role in cancer treatment. In the future, the quality of life will be a key consideration and methods are being sought to boost the quality of life for cancer patients. Cancer treatment is advancing and the 5-year survival rate has also increased considerably in recent years, rising to 70% in Japan, according to the latest results. Improvements in pediatric cancer have also been similarly significant.

K.W. (Center for Kampo Medicine, Keio University School of Medicine) stated that it is probably advisable to separate younger patients from older patients and tailor care to suit the needs of each patient.

S.N. (Center for International Collaborative Research, Nagasaki University) stated that it is important to distinguish between MDGs and Asian cancer. It is important not to focus unduly on MDGs, as cancer in Asia is a complex issue that goes beyond the MDGs. Japan has the power to influence the WHO and it is very important to work toward other issues in addition to the MDGs. It is important to engage in global networking to boost awareness of the issues.

M.I. (Research Center for Cancer Prevention and Screening, National Cancer Center) stated that it is important to promote better collaboration among Asian researchers. Asia, excluding Japan, used to be an area that received research grants from the West and that data were collected by the West. Japan tended to function separately. However,

it is now essential for everyone in Asia to engage in collaboration and work on common issues.

H.S. (Hamamatsu University School of Medicine) stated that the job of cancer specialists is to look carefully at cancer over an extended period of time. In terms of the pathology of cancer, there are various detailed research projects ongoing in Japan that utilizes data gained from patients. However, it can be said that with the stratification of cancer research and cancer treatment into separate fields, there has been a lack of awareness about the actual applications for cancer drugs. Pathology is a very mature field in Japan and Korea is also engaged in cancer research and treatment on a similar level to Japan, together with disease prevalence and treatment methods that are also comparable. In China, however, there is still a considerable gap between rural and urban areas, although the level already attained in urban areas and the openness of government organization to the use of trial drugs means that there are a number of areas where Japan, China and Korea can collaborate together. If broadband access improves in the future, there is also the promise of telepathology, which will aid pathologists in different countries in sharing information.

J.M. (School of Engineering, Osaka University) stated that the Asia Cancer Forum has focused on the situation in higher level countries. However, in low-income countries, cancer has the power to devastate not only the patient but also the livelihoods of the patient's family members. It is important to highlight such issues that are relevant to low-income countries if there is to be a serious chance of placing cancer in the MDGs.

H.I. (Department of Health and Welfare, Chiba Prefecture) noted that there are enormous differences in the funds spent per patient on treating cancer in various countries. For middle-income countries, with several hundred dollars per year, as opposed to several thousand dollars per year for high-income countries, there are some things that cannot be done, but nonetheless there are a number of possibilities.

F.L. (Tianjin Medical University) praised the great level of development made in Korea. She stated that there is great potential for joint clinical trials among Japan, China and Korea. The customs and lifestyles are different in Japan and China and it is important to follow WHO standards in order for results to be accepted in the international arena. Japan, China and Korea should work together to develop new drugs that are ideal for Asia.

J.K.R. stated that while Japan, China and Korea are the leading countries in Asia, the USA remains the preeminent country in cancer research. It is important to respect the research styles and realities in each country when engaging in collaboration. It is important to engage in comprehensive efforts to educate and train personnel.

H.A. thanked all participants for their insightful comments. Regarding the way forward, in broad terms, it is important to gather information and focus on the issues. It is not the role of the Asia Cancer Forum to provide assistance to low-income countries. The Asia Cancer Forum therefore

needs to examine the weaknesses and strengths of cancer research in Asia and look at how we can share our knowledge with various countries in a meaningful way.

CONCLUSION AND FUTURE DIRECTION FOR THE ASIA CANCER FORUM

During the history of the Asia Cancer Forum, since its inception in 2004, there has been a growing awareness of the importance of cancer as a global health agenda issue. This awareness continues to spread through the international health community and is gathering momentum, as seen by the formation of a number of cancer-related fora and organizations, and the readiness of international organizations to address the issue. As cancer is under the spotlight as a global health issue, now is the essential time to engage in efforts to share an accurate recognition of cancer research and treatment throughout Asia and the wider world.

The Asia Cancer Forum places great emphasis on maintaining contact and collaboration with existing organizations and newly formed international bodies to share awareness and information on cancer-related issues. The mainstream of discussion is now squarely addressing the inclusion of cancer in the MDGs, as evidenced by the preparations leading toward the United Nations General Assembly High-level Meeting on the Prevention and Control of Non-communicable Diseases in September 2011. This is precisely the stance that has been taken by the Asia Cancer Forum in its meetings up to and including the seventh meeting in November 2010. However, as they currently stand, the MDGs frame the issue of health as a development issue, focusing predominantly on mother and child health and infectious diseases. Cancer, on the other hand, is not a poverty-related issue. As the participants at the 7th Asia Cancer Forum have recognized, it is essential to position cancer as a mainstream global health agenda issue. However, the focus should be on international cooperation with countries that are at the epicenter of growing cancer incidence, including middle-income countries in Asia, without recourse to governmental development assistance, which has been the main source of health assistance to date.

At the 7th Asia Cancer Forum, the participants highlighted the important issue of providing care that is appropriate to the budgetary means of each country. It was recognized that while possibilities for countries with an annual budget of several hundred dollars per patient per year will be necessarily more limited than countries with thousands of dollars to spare, there are nonetheless various

options available and the past experiences of frontrunner countries can provide valuable lessons. Participants concurred that the issue of cancer should be decoupled from development issues. H.I. also pointed out that measures to counter cancer, particularly awareness-raising, prevention, early detection and improvement of medical systems, could equally be applied to other NCDs (cerebrovascular disease, cardiovascular disease, metabolic syndrome). This raises the question of whether cancer should be handled as a stand-alone issue in the context of measures that aim to deal with NCDs as a whole.

Whether cancer is treated separately or within the context of NCDs, it is essential to create measures that can be feasibly implemented in each country, duly reflecting resource limitations (budget, human resources and expertise) and for this continued cooperation and information sharing will be required.

In the future, the importance of prevention, early detection and effective treatment will continue to increase, putting pressure on already limited resources in both high- and middle-income countries. In the information age, it is essential to share information through all means possible as a way to maximize resources in all countries and help to counter the increasing threat of cancer in the developing and emerging economies.

LOOKING TO 2011

The 8th Asia Cancer Forum is scheduled to be held in the autumn of 2011, following the High-level Meeting on the Prevention and Control of Non-communicable Diseases. It is anticipated that the outcomes of the UN meeting will present further clarity to the positioning of cancer on the global health agenda and the eighth meeting of the Asia Cancer Forum will aim to further distill discussions on how the diverse countries of Asia can cooperate in research and actions that will help to tackle the spread of cancer in the region.

Conflict of interest statement

None declared.

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Meeting Report

The 6th Asia Cancer Forum: What Should We Do to Place Cancer on the Global Health Agenda? Sharing Information Leads to Human Security

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This forum discussed issues relating to the inclusion of cancer on the global health agenda, with the ultimate aim of achieving human security for all people. The forum discussed what methods are available to the cancer community in attempts to create a common data system for the rapidly growing Asian region. Discussions also focused on the preparations that can be made to consider and respond to the obstacles to the creation of an Asia-wide data and information network. It was also noted that in order to create a cancer information network, support would need to be provided to low- and middle-income countries and efforts made to ensure that data are comparable.

Key words: cancer information network – MDGs – human security – data comparability

OVERVIEW

The Asia Cancer Forum is a grouping that aims to discuss cancer science and policy issues among Asian countries. The basic concept of the forum is that discussion will enhance sharing and awareness of the issues and each of the participants will gain their own take-home message to apply to their own activities as the outcomes of the forum. The forum is operated through the research funds of the participating members and receives support in the form of Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan, as part of the Third Term Comprehensive Control Research for Cancer or its ongoing work to create an Asian network. The organizer of the forum is N.K. and it is chaired by H.A., both of the

Research Center for Advanced Science and Technology (RCAST), the University of Tokyo.

The origins of the Asia Cancer Forum date back to 2004 when a group of Asian researchers launched a platform called the Asia High Technology Network to discuss issues in the field of medicine. The grouping engaged in discussions on the formation of an Asia Cancer Information Network. From 2008, the name of the research platform was changed to the Asia Cancer Forum and the first two meetings were held thereafter. The third meeting was held in February 2009, on the theme of ‘Health, Information and Development’. The third meeting was held jointly with SciDev.Net and saw discussion focus closely on issues relating to the setting of the global health agenda. The fourth meeting was held in April 2009 under the theme of

'Asian Challenges in Shifting the Disease Burdens'. In November 2009, the fifth meeting was held in collaboration with the 20th Asia Pacific Cancer Conference (APCC) under the theme of 'What Should We Do to Raise Awareness on the Issue of Cancer in the Global Health Agenda?' The meetings to date have concentrated on ways to share information among Asian research colleagues, thus raising awareness of the importance of including cancer on the global health agenda.

The Sixth Asia Cancer Forum was held in conjunction with the World Cancer Congress UICC 2010, on 21 August 2010, in Shenzhen, People's Republic of China. The meeting consisted of two sessions consisting of six special presentations, followed by detailed discussions. Approximately 60 people were present and active discussions took place. The forum was organized by H.A. and N.K. (RCAST, the University of Tokyo). Invited speakers included H.S. (Hamamatsu University School of Medicine), A.N. (Chiba Cancer Center), T.M. (National Institute of Biomedical Innovation) and J.M. (Osaka University). Also in attendance were Joe Harford [National Cancer Institute (NCI)], Julia Schneider (NCI), X.H. (Chinese Anti-Cancer Association, President of World Cancer Congress UICC 2010), Andreas Ullrich (World Health Organization), David Hill (UICC) and I.A.W. (Asian and Pacific Federation of Organization for Cancer Research and Control).

INTRODUCTION TO THE ASIA CANCER FORUM

N.K. (RCAST) gave an introduction to the ongoing activities and initiatives of the Asia Cancer Forum. She noted that the incidence of infectious diseases in developing countries and the delay in formulating measures to respond to these diseases are recognized as issues requiring the attention of industrialized nations. Accordingly, infectious diseases are given due recognition on the global health agenda. However, cancer has still to gain the recognition it rightly deserves in the world of global health. This is due to the fact that it is generally viewed as a disease specific to individuals in industrialized nations, which occurs as a result of the individual's approach to personal health management.

Last year, the Fifth Asia Cancer Forum discussed issues relating to cancer and concluded that the highest priority should be for expert groups to share a common recognition of the necessity for cancer to be raised on the global health agenda. In the international community, there has also been increasing recognition of the necessity to 'begin discussion on placing cancer on the global health agenda', as evidenced by the Resolution of the United Nations on 13 May 2010 to hold a United Nations General Assembly Summit on Non-Communicable Diseases (NCDs).

However, the results of a survey implemented by the Asia Cancer Forum in April 2010, on the occasion of the 101st Annual Meeting of the American Association for Cancer

Research (AACR), entitled 'Survey on Inclusion of Cancer in the Global Health Agenda', showed that interest in this issue is not particularly high among a great majority of specialists. Discussion on the inclusion of cancer on the global health agenda does not stop merely at the advocacy of humanitarian principles. In fact, what is needed now is a move away from the linear debate such as that which has dominated discussions of aid to developing nations in the past, and a move toward more complex projections. Therefore, it is necessary to gain the broad participation of cancer researchers in working to decipher the current challenges faced by industrialized nations, which could then be utilized in assistance to developing nations. In other words, it is necessary to establish a framework for resolving issues that face industrialized nations.

The world is now in an era in which developments in health innovation have a significant impact on the direction for global health.

In the initial stages of the genome-wide association study, it was thought that genetic differences by race increased the predisposition to the occurrence of a particular disease. However, as research has advanced, it has shown that although there are some statistics differences among races according to the genetic background, the genetic factors predisposing a person to the occurrence of disease are clearly shared by all humankind. In other words, any careful observations made in one specific region of the world are relevant to other regions.

Owing to the tremendous improvements in genome analysis capabilities, it is now possible to analyze genetic information to an incredibly detailed level. Furthermore, information technology (IT) has enabled quantitative tracking of the vast amounts of medical-related data that are created in the modern world. By continuously and automatically collecting and gathering information from various sources, including clinical data and medical records, and using this information to realize the creation of a system that would produce the required evidence for the purpose of providing each patient with the most appropriate and latest medical treatment, research could be used in a synergetic partnership with treatment. Through such technological breakthroughs, it would be possible to search out information relating to the culturally diverse acquired lifestyle customs that exist in Asia, even in persons of similar race, and work to reduce risk factors and even help to prevent further epidemics. It is for this reason that rather than basing research on persons of ethnicities removed from Asia, careful study of the fine differences that exist among the races and nationalities of the Asian region would result in a closer understanding of the nature of diseases in humanity as a whole.

Infectious diseases are characterized by their tendency to infect many people, while the variation in the disease itself is not so great. However, non-communicable diseases, and cancer in particular, have the characteristic of presenting differently from person to person. In other words, it can be seen that 'to understand cancer it is important to look at the

differences among individuals'. In a region with genetic similarities, in which a diversity of acquired lifestyle customs co-exist, would it not be possible therefore to gather significant data through cohort research in the region?

Progress in science bestows upon people the promise of limitless possibilities and the means to live longer. Humankind has devoted much time and effort in the fight against disease.

In the near future, the international community is likely to face an unjust situation in which some people with the same disease will be cured while others will suffer and die.

It is this grave reality that must be addressed.

The Asia Cancer Forum bases its activities on the Universal Declaration of Human Rights, which states that everyone has the right to share in scientific advancement and its benefits equally. In aiming to utilize scientific advancement to address the issue of what we can do to ensure that the challenges that have been faced by industrialized nations are not faced by developing nations, the Asia Cancer Forum is engaging in discussion on the challenge common to both industrialized and developing nations, namely the inclusion of cancer in the global health agenda.

SESSION 1: INFORMATION FROM THE HUMAN BODY

H.A. (RCAST) opened the meeting by requesting comments from Andreas Ullrich (WHO) and David Hill (UICC). Andreas Ullrich noted that the WHO is working very hard to include cancer in the context of NCDs on the global health agenda. What needs to be done on a global scale is exactly what is happening in the Asia-Pacific region in fora like the Asia Cancer Forum, and these activities are very much in line with WHO strategies and policies. David Hill noted that the Asia Cancer Forum is a series of important discussions on the issue of cancer. He stated that the UICC is a global organization, but has a particular concern about cancer control in low- and middle-income countries, many of which are in Asia. There is enormous potential for cancer control, which is currently not being fully implemented. As a species, human beings are very wasteful of the benefits of discoveries. We are not very good at implementing the benefits of discoveries as rapidly, effectively and equitably as we should. Forums such as the Asia Cancer Forum, which focus not only on research and discovery, but more importantly focus on delivering the benefits of research and discovery to populations, are extremely important and are to be commended. The solutions to cancer control lie in people connecting with each other and with their communities to implement the benefits of knowledge that we already have, and that is exactly what the Asia Cancer Forum is doing here.

H.A. presented the concept for this Asia Cancer Forum. The previous APCC was held in Japan and resulted in the issuance of the Asian-Pacific Consensus Statement by

working groups, which aims to improve cancer health science in the Asia-Pacific region. At this discussion last year, it was concluded that cancer must be on the global health agenda and the Asia-Pacific region is ready to work toward this goal. The issues being currently faced are a rapid increase in population in Asian countries, an aging society and increased longevity, together with increased speed in diagnosis. For example, the population of China has a different demographic to that of Japan, but it will gradually come to look like the demographic pyramid of Japan in the future. Expenditure is also rapidly increasing in Asia. Comparisons between the E7 and G7 countries show that medical expenditure is rapidly increasing in E7 countries. Japan has a track record of good healthcare and low spending in terms of GDP. The low spending in Japan has created a number of issues, particularly with regard to the quality of life for medical staff. In other words, Japan has faced a number of cancer issues ahead of other Asian countries and Japan could provide a source of reference for other countries that will face these issues in the future. The aim of the Asia Cancer Forum is to come up with good proposals.

N.K. noted that 'Genetic Solidarity and Altruism' is a powerful phrase that features in the 'Inside Information' documents of the Human Genetics Commission (HGC) of the UK. The progress of innovation means that the significance of holding information and data is changing greatly. What is most important, however, is to ensure that each and every person transforms their awareness about the importance of information in an innovative world.

The Asia Cancer Forum is a body that is committed to strategic analysis in the area of cancer research. The current objective of the Forum is to achieve the inclusion of cancer in the Millennium Development Goals (MDGs) of the United Nations. A long-term perspective must be taken that looks ahead to the issues that will face future generations. It is important to start to consider the design of a social system for collecting and storing the information and data we ourselves possess.

PATHOLOGY NETWORKING IN ASIA

H.S. (Hamamatsu University School of Medicine) noted that cancer diagnosis is based on histopathological pictures and human pathology and cancer diagnosis is a mature scientific field. Histopathological language is common to all oncologists and other cancer specialists and it is now possible technologically to present histopathological pictures. Data can be stored and uploaded on a virtual slide website for joint use. Using this website, scientists worldwide could input their own opinions. Archives stored in digital format can last for almost forever. The virtual slide website is easy to use and browsable. There are many folders on the website featuring histopathological archives, for educational and research purposes, as well as for quality control. Each hospital can send images to a central hospital for diagnosis and compare images among multiple hospitals. The quality of the pictures

is much higher than conventional cameras. With high-speed Internet, it is possible to scan images to high resolutions. For virtual slides, no microscope is necessary, only a high-resolution CCD camera. The problem at the moment we face concerns Internet speed. Eventually, with the dissemination of broadband, this system will be able to be further improved around the region. Scanners are installed in 300 institutions at the moment. Histopathological diagnosis can therefore be performed 24 h around the clock using the worldwide network. In order to expand the network further, it will be necessary to develop infrastructure, including high-speed broadband Internet.

URGENT DEMAND TO ESTABLISH ASIAN NETWORK OF PEDIATRIC BIO-RESOURCE AND TUMOR BANKS FOR BETTER CURE OF THE SICK CHILDREN

A.N. (Chiba Cancer Center) talked about the urgent demand to establish bio-resource and tumor banks in order to better cure sick children. The cure rate of pediatric cancer is very low in many countries in Asia. Epidemiology of childhood cancer in developing countries is largely unknown. It is not known what genetic and environmental factors affect pediatric cancers, in contrast to the knowledge available on adult cancer. It is important to establish a standardized therapeutic and diagnostic system, which would be helpful for the development of epidemiology of pediatric cancers. In 2008, at the meeting of the Advances in Neuroblastoma Research (ANR2008) held in Chiba, Japan, the Steering Committee and the Advisory Board Committee of the ANR Association decided to take an action to establish the international neuroblastoma tumor bank (INTB). The INTB task force includes the establishment of a standardized diagnostic and database system. Neuroblastoma is a very enigmatic tumor, with most being very aggressive. Prognosis is very poor, even now. In order to solve this problem, a staging system was proposed. In order to promote new translational research in the field of cancer, it is necessary to establish a tumor bank system. More than 90% of neuroblastoma tumors in Japan are being sent to Chiba University for analysis. Chiba Cancer Center engages in genomic analysis of these tumors. Efforts are being made to propagate our standardized system to other countries in Asia. All countries agreed to establish a tumor bank; however, the central tumor bank and molecular diagnosis systems are still immature in Asian countries.

WHY DO WE NEED GLOBAL COLLABORATION IN CANCER RESEARCH? ESTABLISHING CROSS-BORDER TRANSFER OF RESEARCH MATERIALS AND INFORMATION

T.M. (National Institute of Biomedical Innovation) introduced one example of networking and commented on why a network is required, particularly in the Asian context. NCI is working to develop a bio-bank system in the USA. This is a very important attempt to share information and materials among cancer researchers, although it is currently limited to

within the USA. Best practices are also issued by the NCI, the first version being issued in 2007. Diagnosis and treatment is not the end of a process, it should be the start for the next generation of research. It is therefore important to achieve integrity between clinical practices and research activities. The NCI also focuses on biomarkers, with the aim of providing transcripts for future use. The common practice for conventional medical research requires a large number of medical researchers and specialists. Researchers tend not to see the bigger picture behind research and it is therefore important to provide transparency in large projects so that researchers can understand their place in the research context. The creation of an international network would therefore be very important. A greater degree of cross-border fluidity is required, working on the already good level of interaction between cancer specialists across borders.

SESSION 2: INFORMATION AS IT SIGNALS

GLOBAL STRATEGIES FOR GENOME AND CELL-BASED INFORMATICS: HIGH-PERFORMANCE DNA SEQUENCING AND EXPRESSION ANALYSIS OPEN A NEW AREA

J.M. (Osaka University) explained the need for an Asian network from the viewpoint of engineering. Fighting against cancer is not simple. Everyone in the pharmaceutical industry is now seeking how to control the pathways and molecular systems of cancer cells. We require huge knowledge in order to achieve this aim, as cancer molecules have an enormous number of variations. Four-dimensional data are required to identify cancer pathways. In our laboratory, we have 200TB of data processing capacity, in order to engage in DNA processing, which provides us with a great deal of data. In Okinawa, we have 10 GB sequencers. We know that medical research is already at a very high level, but R&D remains at a low level, as a part of total expenditure. We therefore have to have more information-based medical systems. We need a system that all stakeholders would be able and ready to use. We have been working on the creation of a network and would like to ask you to join us in our efforts.

TACKLING THE 'LIFESTYLE-RELATED CANCER' WITH CUTTING-EDGE IT

M.A. (University of Tokyo) talked about how to build consensus and share information using IT. Aging society is a serious issue as people are susceptible to other diseases in addition to cancer. In general, the collection of information data is generally done from the bedside. The next-generation system would have to be an interactive system. Cutting-edge systems including bar-code systems and wireless devices would help to create and disseminate data. Another issue is how to gather verbal information using IT. Next-generation data entry systems will need to incorporate measures for gathering verbal information in data format. Cloud

computing could solve issues of data storage in the future, as the storage capacity using cloud computing is virtually limitless and would enable further collaboration, including data entries from patients' homes, etc. If cloud computing is to be used, it is essential that the systems are secure and trusted.

DISCUSSION

H.A. (RCAST) noted that it is essential that all Asian countries share information, technology and knowledge. He invited comments from other participants.

X.H. (Chinese Anti-Cancer Association) noted that Asia needs a forum to focus on the problems facing Asia. Fifty percent of new cancer cases annually occur in Asia, and from the presentations made at the 21st UICC World Cancer Congress, it is known that 80% of new cases of cancer are from low- and middle-income countries, like China, India and Pakistan and other countries in Asia. The issues raised by the presenters are very important and require action. Although there is a lot of knowledge and consensus on most cancers, we still need further information and consultation on some forms of cancer, including pediatric cancers, leukemia and central nervous system cancers, for example. The possibilities for medical consultation through the Internet would be of benefit not only for Asia but for the world, and would facilitate diagnosis for patients and help to diagnose and identify the correct therapies for patients and save their lives. The issue of a tissue bank is also very important. Six years ago, with the support of the National Foundation for Cancer Research (NFCR) from the United States, a Joint Tissue Banking Facility was opened at the Tianjin Medical University Cancer Institute and Hospital in China. Right now there are about 40 000 specimens. An Asian network is essential and Japan is leading the way on this project.

H.S. (Hamamatsu University School of Medicine) noted that Chinese pathologists have many more cases than ordinary Japanese pathological institutions, maybe due to the numbers of people who have variations of tissues. The Internet is a very comfortable way of developing relationships and colleagues in China and Asia should be encouraged to continue to develop such consultation systems.

Joe Harford (NCI, USA) pointed out that through the practice of tele-pathology, it is possible to have samples read in the USA that were collected in Japan during the night and thereby operate around the clock. In contrast, it is instructive to look at the situation that was encountered with pathology services in Ghana. When the Breast Health Global Initiative visited Ghana, the breast pathology reports were taking 6 months to complete, from the time the samples were collected, until the pathology report was submitted. The idea of getting a report in 18–24 h is very different from waiting for 6 months. Tele-pathology does have a great deal of potential for assisting low- and middle-income countries, where there are few pathologists. It is therefore incumbent on the USA

and the Asian region to be thinking about how these technologies can be used to assist the low- and middle-income countries where there are no or few pathologists. This could be in the form of training, or it could be in the form of reading the samples. In the case of Ghana, there was a pathologist in Norway who agreed to train the Ghanaian pathologists so that it became possible to get a much quicker pathology report as a result of training. However, in this case, it required North–South cooperation. Efforts should be made to share resources with the low- and middle-income countries.

A second issue raised by Joe Harford was that of tumor banking. The exchange of samples across borders presents significant problems. Each country has its own restrictions on how samples flow across borders. Hypothetically, there is no need to ever ship a sample across a border. All that is required is to have comparable sample collection everywhere, and the equipment to analyze those samples everywhere, and then the information could be shipped across borders. It ought not to be necessary to ship samples across borders, theoretically. This would require a certain amount of standardization. One of the things that the NCI has been engaged in with the bio-banking effort is best practices and standardization, which is an ongoing effort. In order to ensure that there is comparability across borders requires a small number of samples collected in Japan, for example, to be tested in China or the USA, so that you can assure yourselves that comparability has been achieved. Once comparability has been assured then you ought not to need to ship samples. All of the countries that are involved in a network of collaborative bio-banking should be encouraged to work with governments, and perhaps with the WHO, to make these provisions that would at least allow for these small studies in comparability to be implemented.

The term 'comparability' is an interesting word, but it does not necessarily mean uniformity. This particularly applies to informatics platforms and cancer registries and the software that is used for cancer registries. These are not uniform, but they can still be comparable. Databases in particular do not have to be uniform, but it is important to create 'adaptors' that would enable data gained in one country to be usefully compared in another country. It is not expected that the world will uniformly follow US or other standards, but in the interests of collaboration, the opportunity to adapt between systems and be able to compare is essential.

Julia Schneider (NCI, USA) congratulated the Asia Cancer Forum for specifically talking about developing platforms for enhancing collaboration within and outside of Asia. There is tremendous potential in the age of genomics and proteomics to do meta-analysis of large collections of specimens. It is important to ensure that specimens are comparable. After the initial quality control is implemented, it makes sense for specimens to be analyzed in the country in which they were gathered. It is very exciting that these sorts of issues about creating and developing platforms and infrastructure are being discussed in this forum.

With regard to the NCI best practices, the new version is now published and is available on the website for comment. NCI is very actively interested in receiving comments on this new version. The process that was used for developing the NCI best practices was very focused on the USA. It would be good to continue the dialogue about developing standards that can be implemented effectively in both Asia and the USA and other parts of the world. In the USA alone, many challenges were encountered in terms of the way that different institutions were engaging in analysis, both from the technical side and also the ethical and legal issues (informed consent, privacy protection etc.). These issues become even more complex in the context of cross-border collaboration, but it is extremely important to develop and facilitate such international collaboration.

M.A. (University of Tokyo) noted that with cutting-edge IT, it is possible to create information not only for cancer but also for diabetes and other diseases. Lifestyle-related cancer is a chronic disease. The cost for hemodialysis and treatment of cancer is very expensive. It would be possible to use cutting-edge IT to create systems that would be applicable to a variety of lifestyle-related diseases.

I.A.W. (Asian and Pacific Federation of Organization for Cancer Research and Control) reported that in the Southeast Asian context, it is necessary to look at more fundamental issues, because there are discrepancies in the region with standards of health care. There are some parts of the region where there are no people who diagnose or even treat patients. In order to look at the cancer agenda, we need to look at the issue in global terms. For example, take a country like Malaysia, in Kuala Lumpur, there are 15–20 cancer centers within a radius of 25 km, but in other regions, there are no physicians who are qualified to provide cancer care. These are issues that need to be examined. Hospitals treating cancer in the Southeast Asian region have to endure a tremendous burden, where, in some cases, patients have to share beds in a cancer hospital and 200–300 patients are having chemotherapy in a single day. It is therefore important to examine the manpower problem. Part of the issue here is improving the standards of diagnostic care, sharing of pathology and maybe radiology reports through the Internet, but we must also consider how we address the issue of manpower shortage. There are parts of the region where there are no cancer specialists. It is important to think about these important issues of manpower and consider how we can improve this from an Asian perspective.

Andreas Ullrich (WHO) noted that it is important that the Asia Cancer Forum is an open platform for all countries, including low-, middle- and high-income countries. Linking all these countries toward a common goal is extremely important. One of the major drivers in decision-making in the political circles is the availability of data. It is important not only to know how many cases of cancer are occurring, but also to know about the number of staff who are available in each country. Also, we must consider the availability of technology, including diagnostic

devices, essential medicines etc. The Asia Cancer Forum could be one that goes beyond the diagnosis of cancer and could be a forum for collecting data about infrastructure. It could provide information through the Internet and other tools could be developed (or are already developed by the WHO) about capacity in countries. This information could then be combined not only for academic purposes but also for a policy forum, where intelligence is translated into policy proposals to politicians. The politicians could then be shown data about incidence of cancer, mortality and survival rates etc. Survival data are very strong drivers in political decisions, as we have seen in Europe. They are not available universally across the Asian region. There is great potential for this forum to set an agenda for what needs to be achieved in terms of political decision-making and will be required to achieve that target.

Massoud Samiei [International Atomic Energy Agency (IAEA)] noted that in order for donors to invest in cancer, it is important to have convincing projects to show that something can be done about cancer. Cancer is perceived as a very expensive disease. The IAEA works with the WHO in many developing countries, including in Asia, to establish cancer centers, and often donors ask about investing in cancer as it is a very expensive disease. In order to get cancer on the MDGs, it is essential to show that there are strategies and solutions that are cost-effective. With a little investment, progress can be made in terms of prevention, screening programs and focusing on specific types of cancer. For this, we have already created examples through the IAEA programs across the globe. The IAEA could collaborate with the Asia Cancer Forum to provide information for the creation of a proposal to submit to the UN. Donors are only interested in cost-effective solutions. The IAEA has pilot projects in eight countries currently and could share these results with the Asia Cancer Forum.

CLOSING

H.A. and N.K. thanked the speakers and participants for their insightful comments and active participation. In closing, it was noted that the ultimate goal is to utilize advances in innovation to create a large database of knowledge and a global network for analyzing data and sharing information. To this end, it is essential to make efforts to collect all kinds of medical information. The opinions raised at the forum concerning means of sharing data and raising awareness among specialists and patients alike about the importance of medical information in the fight against cancer demonstrated that there is a general awareness of the issue. It was recognized that further efforts must be made to create awareness among specialist organizations of the value and necessity of setting the global health agenda for the sake of scientific development. Approaches must also be developed that enable countries and regions at different levels of development to share data in a comparable manner.

ROAD TO 7TH ASIA CANCER FORUM

The discussions at the 6th Asia Forum identified a number of key issues that need to be tackled if a comprehensive cancer network is to be achieved. Knowledge gaps exist between the current status of cancer research and treatment in front-runner countries, such as Japan, and the perception of issues in developing and emerging countries. It was recognized that the issue of obstacles to sharing common challenges is one that requires further discussion and analysis. The Asia Cancer Forum will continue to examine means for sharing information in a meaningful and comparable manner. In particular, the role of IT in opening up cancer issues for global health consideration will be focused on in future meetings, with input being sought from policy-makers in government and from the private sector, including pharmaceutical companies. The 7th Asia Cancer Forum is

scheduled to be held on 3 November 2010, with invited speakers from the Asian region and major pharmaceuticals coming together to discuss the way forward for a comprehensive cancer network in Asia. With the participation of representatives of academia, government and industry at the 7th Asia Cancer Forum, it is anticipated that the technical issues, specifically relating to knowledge and know-how gaps between front-runner and developing countries, will be further discussed, with a view to crystallizing a future path for a comprehensive cancer information network in the Asian region.

Conflict of interest statement

None declared.

A Phase I Study of Personalized Peptide Vaccination Using 14 Kinds of Vaccine in Combination With Low-Dose Estramustine in HLA-A24-Positive Patients With Castration-Resistant Prostate Cancer

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BACKGROUND. To evaluate the safety, tolerability, immune response, and antitumor activity of a combination of personalized peptide vaccination (PPV) and estramustine phosphate (EMP) in patients with castration-resistant prostate cancer (CRPC).

METHODS. In a phase I dose-escalation study, four peptides showing the highest levels of peptide-specific immunoglobulin G (IgG) to 14 vaccine candidates (ITK-1) were subcutaneously injected every week in three different dose settings (1, 3, and 5 mg per peptide) for 6 weeks with a low dose of EMP, and the patients were followed by maximum 2 years extension study either weekly or bi-weekly six times PPV as one course with a low dose of EMP.

RESULTS. Fifteen patients were enrolled in the phase I study. No serious treatment-related adverse events were observed. The most common adverse events were grade 2 skin reactions at the injection sites. The maximum acceptable dose of ITK-1 was 8.643 mg. There were no treatment-related systemic adverse events of grade 3 or more, and maximum tolerated dose could not be determined. Cytotoxic T lymphocyte responses measured by interferon- γ release assay were boosted in 10 of 15 (67%) patients, and IgG responses were boosted in 7 of 15 (47%) patients. Twelve patients proceeded to the extension study, and the median survival time was 23.8 months during a median follow-up of 23.8 months.

CONCLUSIONS. PPV treatment for HLA-A24 positive patients with CRPC could be recommended for further stages of clinical trials because of its safety and the higher frequency of boosting immune responses. *Prostate* 71: 470–479, 2011. © 2010 Wiley-Liss, Inc.

KEY WORDS: personalized peptide vaccine; immunotherapy; phase I study; estramustine phosphate

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INTRODUCTION

In the initial trials, peptide-based vaccine treatment of cancer patients rarely induced clinical responses and the levels of immune responses was low, indicating that the classical type of peptide vaccines did not have a promising future in the treatment of advanced cancer [1,2]. However, there have been slow but substantial advances in peptide vaccines and dendritic cell (DC)-based vaccines with regard to both clinical responses and immunological markers [3–12].

We previously reported that repeated multiple peptide vaccine regimen planned according to the pre-existing immunity (personalized peptide vaccine: PPV) could prolong the overall survival of patients with advanced cancer, and IgG specific to each peptide can frequently be detected in pre- and post-vaccination plasma [13]. In the previous trial, PPV was administered in 113 patients with advanced cancer, and the levels of peptide-specific cytotoxic T lymphocyte (CTL) precursors were measured by the interferon (IFN)- γ release assay and those of anti-peptide immunoglobulin (IgG) were estimated by enzyme-linked immunosorbent assay (ELISA). The level of anti-peptide IgG was a laboratory marker that predicted clinical responses to the PPV with a positive relationship to overall survival. Further, we showed that 58 patients with castration-resistant prostate cancer (CRPC) treated with a combination therapy of PPV and a low dose of estramustine phosphate (EMP) survived for a relatively long period of 17 months, which was comparable with the results of chemotherapy with docetaxel, and serious adverse events occurred less frequently in the study [4].

ITK-1 is a peptide set consisting of 14 kinds of peptide discovered as a HLA class I epitope, which being developed by Green Peptide Co., Ltd. All the 14 peptide candidates can induce CTLs, and each of them can induce HLA-A24-restricted and tumor-specific CTL activity in peripheral blood mononuclear cells (PBMCs) of cancer patients [14–18]. We have conducted a phase I study on PPV and low-dose EMP in HLA-A24-positive patients with CRPC in order to define the safety, tolerability, and immune and prostate-specific antigen (PSA) responses of this drug combination.

PATIENTS AND METHODS

Patients

This was a multi-center study and approved by each institutional review board (IRB) that evaluated it from the viewpoint of the science and ethics in all four hospitals in Japan before the initiation of the study. Patients who had a histological diagnosis of prostate

adenocarcinoma (PC) and progressive disease (PD) by diagnostic imaging (computerized tomography; CT, magnetic resonance imaging; MRI or bone scintigraphy) or PSA after both androgen deprivation therapy either by castration or with luteinizing hormone-releasing hormone (LHRH) agonists and anti-androgen therapy, as well as oral EMP treatment were eligible. PSA progression was defined as at least three consecutive rises in serum PSA taken over 2 weeks apart, in the setting of castration levels of testosterone. Patients were required a washout period of at least 4 weeks before the first vaccination after the completion of prior hormone therapy, hormone-chemotherapy, chemotherapy, or immune therapy. Anti-androgen therapy was discontinued for at least 4 weeks before the first vaccination for patients receiving flutamide and 6 weeks for those receiving bicalutamide. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, HLA-A24-positive type, and serum testosterone level ≤ 50 ng/dl, and were maintained on LHRH agonist therapy or castration. Adequate organ functions were required and were defined as white blood cell count $\geq 3,000/\text{mm}^3$, lymphocyte count $\geq 1,200/\text{mm}^3$, hemoglobin ≥ 9 g/dl, platelets $\geq 100,000/\text{mm}^3$, total bilirubin ≤ 1.5 mg/dl, AST and ALT $\leq 2\times$ (upper normal limit), and serum creatinine ≤ 1.4 mg/dl. Patients with comorbidities including serious cardiovascular, hepatic, nephritic, and hematological diseases \geq grade 3 of Common Terminology Criteria for Adverse Events (CTCAE), serious gastric ulcers, and infectious diseases with antibiotic treatment, were excluded. Radiation therapy or immunosuppressive treatment using a systematic steroid within the last 1 year was not permitted. All patients gave written informed consent approved by each IRB.

Study Design

This was a phase I open-labeled dose-escalation study. After a pre-vaccination measurement of peptide-specific IgG in the plasma of patients reactive to 14 kinds of vaccine candidate peptides (ITK-1) with the ability to induce CTLs, patients were treated with 6 weekly subcutaneous administration of the top four peptides showing the strongest antibody responses at three different dose settings (1, 3, and 5 mg/peptide), with daily oral EMP 313.4 mg in the phase I study. This was followed by a maximum of 2 years in an extension study of six PPVs either weekly or bi-weekly as one course. All patients were treated at the hospital during the first 1 week followed by outpatient clinic visits. ITK-1 consists of 14 kinds of peptides: SART_{293–101}, SART_{3109–118}, Lck_{208–216}, PAP_{213–221}, PSA_{248–257}, EGF-R_{800–809}, MRP_{3503–511}, MRP_{31293–1302}, SART_{2161–169},