МЕДИЦИНСКИЕ АСПЕКТЫ ЧЕРНОБЫЛЬСКОЙ КАТАСТРОФЫ

MEDICAL AID AND RESEARCH PROJECTS FROM NAGASAKI ON RADIATION HEALTH EFFECTS AROUND CHERNOBYL

SHUNICHI YAMASHITA

Department of Molecular Medicine Atomic Bomb Disease Institute
Nagasaki University Graduate School of Biomedical Sciences

The medical cooperative projects from Nagasaki to the former USSR have been performed in mainly two regions: Chernobyl and Semipalatinsk since 1990 and 1995, respectively. What we should do here in Nagasaki and also from Nagasaki will be discussed at the standpoint of humanitarian medical aid and scientific research collaboration using different channels of governmental and non-governmental cooperative linkages. The 21st Center of Excellence (COE) program of «International Consortium for Medical Care of Hibakusha and Radiation Life Science» established in Nagasaki University can serve our knowledge and experience much more directly in relation to the radiocontaminated areas in the world, and indeed contribute to the lessons learned from Chernobyl and also to the newly establishme of Network of Excellence (NOE) for Radiation Emergency Medicine under the auspices of the WHO-REMPAN.

Within the frame of the International Consortium of Radiation Research, a molecular epidemiology of thyroid diseases has now been conducted in our departments. The clue of radiation-associated thyroid carcinogenesis may give us a new concept on experimental and epidemiological approaches to low dose radiation effects on human health, including internal radiation exposure.

Key words: radiation, health effects, Chernobyl, Medical Aids.

ПОСЛЕДСТВИЯ АВАРИИ НА ЧЕРНОБЫЛЬСКОЙ АЭС: МЕДИЦИНСКАЯ ПОМОЩЬ И НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЕ ПРОЕКТЫ ОТ НАГАСАКИ

Суници Ямасита

Кафедра молекулярной медицины, институт заболеваний атомной бомбардировки, высшая школа биомедицины университета г. Нагасаки.

Совместные медицинские проекты между Нагасаки и республиками бывшего СССР были сосредоточены, главным образом, на двух направлениях: Чернобыле и Семипалатинске, начиная с 1990 и 1995 годов соответственно. Работу, осуществляемую в Нагасаки и исходящую из Нагасаки, следует рассматривать с точки зрения гуманитарной медицинской помощи и научно-исследовательского сотрудничества с использованием различных каналов правительственных и неправительственных совместных связей. 21-я программа Центра Превосходства (Centre of Excellence, COE) «Международный Консорциум Медицинской помощи Хибакуша и радиационной медицины», разработанная в университете Нагасаки, может непосредственно расширить наши знания и опыт в области регионов мира, подвергшихся радиоактивному заражению, извлечь уроки из Чернобыля, а также послужить базой для недавно созданной Сети Превосходства (Net of Excellence, NOE) экстренной радиационной медицины под эгидой ВОЗ-РЕМПАН.

В рамках Международного Консорциума радиационных исследований наши кафедры в настоящее время выполняют работу по молекулярной эпидемиологии заболеваний

щитовидной железы. Выявление взаимосвязей между карциногенезом ЩЖ и радиацией может дать нам новую концепцию экспериментальных и эпидемиологических подходов к изучению воздействий малых доз радиации на человеческий организм, включая дозу внутреннего облучения.

Ключевые слова: радиация, воздействие на здоровье людей, Чернобыль, медицинская помощь.

Introduction

Acute manifestations of an atomic bomb disease are well described in Hiroshima and Nagasaki victims and categorized into three entities: burns, external injuries and severe radiation-induced injuries. The late effects of the atomic bombings as well as emergency radiation medicine have been carefully analyzed and the risk of late-onset malignancies has been demonstrated for various organs [1]. Such a tremendous amount of data (knowledge and experience) has been very useful for the treatment of radiation victims of Chernobyl and Semipalatinsk. However, the type and dose rates of radiation exposure are completely different among Nagasaki, Chernobyl and Semipalatinsk. Therefore, molecular epidemiology is urgently needed to be established in the field of Radiation Life Sciences to clarify the real carcinogenic effect of ionizing radiation on various cells, tissue and organs [2].

During the past ten years, the counterparts of advanced medical institutes in the former USSR made mutual agreements for the exchange in the area of medical science and of specialists with our university: Belarusian State Medical University in Minsk, Belarus, Gomel Medical Institute, Gomel, Belarus, Medical Radiation Research Center of Russian Academy of Medical Sciences, Obninsk, Russia, and Semipalatinsk State Medical Institute, Semipalatinsk, Kazakhstan. Recently, we have established sister university relationships with Institute of Radiation Medicine and Institute of Endocrinology and Metabolism, Kiev, Ukraine. We have also been inviting visiting professors, medical researchers, and postgraduate students from these establishments every year to the Atomic Bomb Disease Institute at Nagasaki University School of Medicine (http//www. med. nagasaki -u. ac j p/renew/inform ation/information e.html). The content of this review article is originally based on the report of the first 21st COE international symposium in Nagasaki University on February, 2003.

Medical Cooperative Projects from Nagasaki to Chernobyl

An overwhelming amount of various radionuclides was released in the environment after the Chernobyl nuclear plant accident, which happened on April 26, 1986 in Ukraine. From Japan, different levels of medical assistance had been involved, but specific medial assistance based on a scientific approach wasn't started until 1991. One of the most comprehensive projects was the Chernobyl Sasakawa Medical Cooperation Project. A direct linkage between Japan and Chernobyl has been established following the donation of modern equipment and various consumables from Sasakawa Memorial Health Foundation to the three countries involved, which made it possible to standardize our protocol of health screening even after the collapse of the USSR. The first 5-year project started from May 1991 had been completed in 1996 and data has been collected on more than 120,000 children [3]. The charactenstic points of this project were the following: children at highest risk to radiation health effects (age at the time of the accident from 0 to 10 years old) were identified, and the screening mainly focused on the possible late effects of radiation was performed using common procedures of thyroid and hematological examinations, and whole body Cs-137 measurement in all the subjects to determine the current radiocontaminated levels and to relieve their anxiety.

Results of this large-scale screening demonstrated that nearly 3% of the children had thyroid abnormalities other than goiter, for which we could perform an echo-guided fine needle aspiration biopsy and cytological diagnosis. Importantly, among thyroid nodules more than 0.5 cm in size with abnormal echo findings there were about 7% of malignant ones suggestive of high incidence of thyroid cancer, especially papillary adenocarcinomas in children around Chernobyl.

The doses of residential direct external exposure due to the accident were low and so there is no evidence of increased rate of childhood leukemia. However, acute internal radiation exposure might be high because of fallout of short-lived radioactive nuclides. Also, a chronic low dose exposure from the radiocontaminated soil and environment should not be neglected.

From May 1997 to April 2001, the second Chernobyl Sasakawa projects have been conducted in Belarus and Russia [4]. Simultaneously, other international organizations such as EU, WHO and NCI have participated in the Chernobyl Thyroid Tissue Bank project (http//www. chernobyltissuebank. com/). Several scientific cooperation projects are now on-going. We really wish to continue a follow-up study of a high risk group of subjects who have already been diagnosed for thyroid diseases, especially nodules, and still live in the radiocontaminated areas around Chernobyl.

This is a special occasion to make a tight linkage between Gomel Medical University and Nagasaki University under the mutual agreement. I really congratulate on the first issue of the publication of the Gomel Medical University. The medical cooperative research projects **will** be established and an exchange program of young scientists will be planned under the auspices of our sister university relationship. Hopefully within Belarus at first Telemedicine project will be completed to further strengthen medical education system as well as medical consultation capacity between Belarussian Medical University in Minsk and Gomel Medical University.

Summary of Joint Research Results in the former USSR

During the past three years, we succeeded to obtain fairly good cooperative research results with the scientists and physicians from the former USSR.

1Our joint project on Chernobyl Thyroid Tissue Bank has been smoothly running in Russia and Ukraine but not in Belarus. In the light of this idea, the establishment of Tissue Bank and/or Blood Bank is now under negotiation with our research counterparts in Semipalatinsk, Kazakhstan.

2The psychosocial problems in local residents around radio-contaminated areas have been analyzed [5]. Separately, the radiosensitivity of younger children compared to adults has been proved, and the dramatic increase of childhood thyroid cancer is mostly likely due to the short-lived radionucletids (radiation fallout) from Chernobyl [6].

3Genetic analysis of short statures in the former USSR has indicated the specific *Prop 1* gene mutation pattern and provided a clue of the etiology of combined pituitary hormone deficiency syndrome [7].

4Our molecular biology study on thyroid carcinogenesis using samples from Semipalatinsk indicated the necessity of research on clarification of radiation-associated signature genes in human thyroid cancers [8]. Our preliminary data on urinary iodine measurement has also been reported [9], indicating the proper supplementation of iodine around Semipalatinsk.

5Low-dose radiation inducible genes have been identififed using cultured human thyroid cells, among of which *hSNK,* a gene encoding serum-inducible kinase may be one of the most promising [10]. We have also investigated the characteristics of intracellular signal transduction in human thyroid cells [11—14]. Furthermore, large-scale deletions of mitochondrial DNA have been demonstrated to be a possible molecular marker of radiation-associated thyroid carcinogenesis [15].

Despite the remarkable findings and research activities listed above, there is a persistent difficulty in obtaining the reliable dosimetrical data from Chernobyl. Therefore, new approaches are urgently needed to overcome the uncertainty of radiation dose evaluation.

Future Scope and Conclusion

Our work of recent years has been going off swimmingly also due to the establishment of a cooperative organization, the Nagasaki Association for Hibakusha's Medical Care (NASHIM) in 1992 (http://www.nashim.org/). Combined with this NASHIM's activity, the 21st COE program of «International Consortium for Medical Care of Hibakusha and Radiation Life Sciences» can promote much more scientific exchange programs and yield more fruitful data on low-dose radiation effects on human health.

We are all «Hibakushsas», which means we are suffering not only from radiation but also from various kinds of environmental factors in our life from the very beginning. Understanding the impact of the environment on mental and physical health of a man gives us a chance to elucidate the importance of a cross-talk between the human body and various environmental factors at the different levels and duration of exposure. We must continue our efforts from Nagasaki to contribute to International Hibakusha Medical Care through the international networks and simul-

taneously educate young physicians and students, especially in the former USSR, to work with us from the standpoint of adherence to the policy of global medical care standardization and universal radiation life sciences with wider perspectives.

The ultimate goal of our department is to identify the molecular signature(s) of radiation-associated human diseases and to develop molecular targeting gene therapy for the malignancies.

LITERATURE

1. *Thompson D.E., et al.* Cancer incidence inatomic bomb survivors. Part II: Solid tumors 1958—1987. RadiaRes 1994; 137: S17—S67.

2. *Yamashita Si, Shibata Y., Namba H., Takamura N., Saenko V.* Molecular epidemiology of childhood thyroid cancer around Chernobyl. Radiation and Homeostasis. eds by Sugawara T, Nikaido 0, Niwa 0. Excerpta Medica 2002; ICS 1236; p201— p205.

3. *Yamashita S., Shibata Y.* (eds) Chernobyl;A Decade. Excerpta Medica 1997; ICS 1156; p 613.

4. *Yamashita S, Shibata Y., Hoshi* M, *Fujimura K*(eds) Chernobyl; Message for the 21st Century.Excerpta Medica 2002; ICS 1234; p354.

5. *Takamura N., Kryshenko N., Masyakin V.,Tamashiro H., Yamashita S.* Chernobyl-induced radiophobia and the incidence of tuberculosis.Lancet 2000; 356: 257.

6. *Shibata* Г., *Yamashita S., Masyakin V.,Nagataki S.* Fifteen years after the Chernobyl ac cident, novel evidence of post-Chernobyl thyroid cancer. Lancet 2001; 9297: 1965—1966.

7. *Fofanova O., Takamura N., Kinoshita K, VorontsovA, Vladimirova V., DedovII., Peterkova V.A.,Yamashita S.* MR imaging of th pituitary gland in children with congrenital combined pituitary hormone deficiency associated with PROP1 mutations.Am J Roentogenol 2000; 174:555—559.

8. *Alipov G., Takamura N., ho M., Pulgro E.,Yamashita S.* Ret/PTC rearrangement in thyroid cancer around Semipalatinsk nuclear testing sites. Lancet 1999; 354: 1528—1529.

9. *Hamada A., Takamura N.. Meirmanov S.,Alipov G., Mine M., Ensebaev R., Sagandikova S.,Ohashi T., Yamashita S.* No evidence of radiation risk for thyroid gland among schoolchildren around Semipalatinsk nuclear testing site. Endocrine J 2003; 50: 85—89.

10. *S-Yoshida Y., Sugiyama . Rogounovitch T,Ohtsuru A., Namba H., Saenko V., Yamashita S.*Radiation-inducible hSNK gene is transcription-ally regulated by p53 binding homology element in human thyroid cells. Biochem Biophys Res Commun 2001; 289: 491—498.

11. *Mitsutake N., Namba* Я, *Shklyaev S., Tsukazaki T., Ohtsuru A., OhbaM., Kuroki T., Ayabe H.,Yamashita S.* PKC delta mediates ionizing radiation-induced activation of c-Jun NH2-terminal kinase through MKK7 in human thyroid cells. Oncogene 2001; 20: 989—996.

12. *Ishigaki K., Namba H., Nakashima M.,Nakayama* 7'., *Mitsutake N., Hayashi T., Maeda S.,IchinoseM., Kanematsu T, Yamashita S.* Aberrant localization of beta-Catenin correlates with over-expression of its target gene in human papillary thyroid cancer. J Clin Endocrinol Metab 2002;87(7): 3433—3440.

13. *Mitsutake N., Namba H., Takahara K.,Ishigaki K., Ishigaki J., Ayabe H., Yamashita S.*Tie-2 and angiopoietin-1 expression in human thyroid tumors. Thyroid 2002; 12(2): 95—99.

14. *Saenko V.A., Rogounovitch T.I, Abrosi-movA.Y., Takamura N., Lushnikov E.F., Namba H.,Yamashita S.* Problem of prevalence of ret/PTC rearrangements in thyroid tumors. Thyroid 2002;12(5): 435—434.

15. *Rogounovitch T.I., Saenko V.A., S-YoshidaY., Abrosimov A.Y., Lushnikov E.F.,RoumiantsevP.O., Ohtsuru A., Namba K, Tsyb A.F.,Yamashita S.* Large deletions in mitochondrial DNA lin radiation associated human thyroid tumors. Can-cer Res 2002; 62: 7031—7041.