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The 450th International Symposium on Therapy

The 450th International Symposium on Therapy was held by the Zoom Webinar on July 15, 2021. Dr. Koichi Ito, Managing Director of the International Medical Society of Japan (IMSJ), presided over the meeting.

The latest treatment of thyroid disease

~ From the aspect of internal medicine and surgery ~

Introductory Message from the Chair

Koichi Ito, MD, PhD
Managing Director, IMSJ

Thank you for coming here today. Our hospital offers the most advanced treatment for thyroid diseases. Now, let me introduce our hospital staff to you.

Firstly, Dr. Ai Yoshihara is the medical director of internal medicine. She will speak about "Hypothyroidism and Pregnancy." Hypothyroidism is predominantly present among women. It often coincides with childbearing age. Previously, pregnancy complicated with hyperthyroidism was a significant issue. But we have resolved it through many years of clinical experience. Nowadays, established evidence suggests that childbirth in a hypothyroid state is likely to impair brain development in children. Therefore, it becomes essential to call a thyroid doctor to cooperate with a fertility specialist and a gynecologist. Our specialists' mission, for now, is to fine-tune the thyroid-stimulating hormone flow while controlling the TSH amount within the typical values. You will hear shortly how the team is trying to exploit their expertise.

Secondly, Dr. Chie Masaki, a staff member of the surgery department, will talk about the "treatment surgery of thyroid cancer." The overwhelming

majority of thyroid cancer is papillary carcinomas with low biological malignancy. A single treatment with surgery can produce an excellent prognosis. Currently, micropapillary cancer with the 1 cm or less central axis is subject to a follow-up observation under a secured medical care system. As to advanced cancer, we have proactively performed total thyroid surgery and internal radiotherapy.

But in some cases, additional treatment is impossible due to insufficient isotope accumulation. Under such circumstances, molecular-targeted drugs have emerged as new cancer therapeutic drugs. We use them aggressively. You will soon hear how we are racking our brains to provide the best treatment.

Lecture I

Hypothyroidism and Pregnancy

Ai Yoshihara
Medical Director of Internal Medicine
Division of internal medicine, Ito Hospital

The reference value ranges of thyrotropin (TSH), free triiodothyronine, and free thyroxine change throughout pregnancy, mainly because of increases in estrogen, thyroid-binding globulin, and human chorionic gonadotropin levels. In the first trimester, maternal hCG directly stimulates TSH receptors, thereby increasing thyroid hormone production and resulting in a subsequent reduction in serum TSH concentration. Thus, women have lower serum TSH concentrations during pregnancy than before pregnancy. TSH reference ranges vary among racial and ethnic groups, and they

greatly depend on iodine intake. Serum TSH measurements remain the principal means of assessing maternal thyroid status, and reference ranges should be based on values obtained in healthy thyroid-antibody-negative pregnant women with optimal iodine intake and no thyroid illness. It is recommended that local population data be used to assess population-based trimester-specific TSH reference value ranges. The upper limit of the normal range of TSH values measured in the first trimester in our hospital is 2.56 μ U/ml.

Overt hypothyroidism during pregnancy has consistently been shown to be associated with an increased risk of adverse pregnancy complications, including pregnancy loss, gestational hypertension, and placental abruption. Thyroid hormone is essential for fetal brain development, which begins early in gestation and is totally dependent on the maternal thyroid hormone that crosses the placenta. One study conducted on pregnant hypothyroid women showed impaired neurocognitive development in their offspring in comparison with the offspring of pregnant euthyroid women. Adequate thyroid replacement with levothyroxine (LT4) prevents the adverse outcomes of pregnant hypothyroid women and their offspring. Subclinical hypothyroidism (SCH) is a condition in which thyroid hormone levels remain within their normal ranges, but the TSH level is above the upper limit of the reference range. SCH during the first trimester has been reported to be associated with increased maternal and fetal complications, including increased rates of fetal loss, pre-eclampsia, placental abruption, and preterm delivery.

A prospective study conducted in Italy reported finding that euthyroid pregnant women who were TPOAb-positive developed impaired thyroid function that was associated with an increased risk of miscarriage and premature delivery., and that LT4 replacement therapy reduced the rate of miscarriage and premature delivery. The same group of investigators conducted a study on TPOAb-negative pregnant women and found a significantly higher rate of spontaneous fetal loss in the women whose TSH levels were between 2.5 and 5 mIU/L in the first trimester compared with those whose TSH levels were <2.5 mIU/L. Based on these findings, the American Thyroid Association and the European Thyroid Association made the goal of LT4 treatment the normalization of maternal serum TSH values to within their trimester-specific pregnancy reference ranges: first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L; third trimester, 0.3–3.0 mIU/L. In 2017, the American Thyroid Association recommended LT4 replacement for TPOAb-positive women with a TSH level greater than the pregnancy-specific reference range, or a TSH level >2.5 μ U/ml when no local specific range is available, and for TPOAb-negative women with a TSH level greater than the pregnancy-specific reference range, or a TSH level >4.0 μ U/ml

when no local specific reference range is available. In addition, the American Thyroid Association recommended LT4 therapy for SCH women seeking pregnancy by means of artificial reproduction technology who had a TSH level elevation to >2.5 mU/L and stated that the goal of treatment is to achieve a TSH concentration <2.5 mU/L.

Thyroid autoimmunity has also been reported to be associated with fetal loss and preterm delivery, and one of the hypotheses proposed to explain these complications is that mothers with thyroid autoimmunity tend to have an impaired thyroid response to human chorionic gonadotropin.

Theoretically, treating SCH by LT4 supplementation should reduce the risk of adverse pregnancy outcomes, but there have been discrepancies among the results of studies on the effect of LT4 supplementation. Some studies have reported beneficial effects of LT4 supplementation, while others have shown no significant effects on miscarriage rates. The Japanese Thyroid Association is currently attempting to develop clinical guidelines for the treatment for SCH before conception and during pregnancy. Further large randomized controlled trials are needed to be able to draw definite conclusions in regard to the treatment of SCH before and during pregnancy.

Lecture II

Treatment Strategy of Thyroid Cancer ~ Now and beyond focused on Molecular Targeting Drugs ~

Chie Masaki MD,
Medical Staff

Department of Surgery, Ito Hospital

Thyroid cancer is well known to have low cause-specific mortality, but morbidity has recently been increasing despite stable mortality worldwide. The problem of “overdiagnosis and overtreatment” has been raised, and restriction of diagnosis by fine needle aspiration cytology and of surgical treatment has been proposed worldwide. “Active surveillance (AS) for low-risk T1aN0M0 papillary thyroid carcinoma”, first advocated in Japan, is now spreading globally.

On the other hand, there are certainly patients with advanced cancer who progress to fatal outcomes, though in limited numbers. Patients with distant metastases have had no other choice than to receive total thyroidectomy followed by radioactive iodine (RAI) therapy until now. The long-awaited molecular-targeted therapy for thyroid cancer started with sorafenib in 2014, followed by lenvatinib and vandetanib, which were approved in 2015. They all are classified

as tyrosine kinase inhibitors (TKIs), with effects on multiple sites of the molecular pathway. These three drugs are now indicated for “unresectable advanced thyroid cancer (RAI refractory in the cases of differentiated cancer)”.

Along with this, postoperative surveillance methods for thyroid cancer patients in the high-risk group are also changing. More frequent morphological evaluation by CT and PET-CT examinations has been performed, and multidisciplinary treatment including surgery and radiation therapy for distant metastases has been actively provided. Pharmacotherapy for thyroid cancer is not indicated only because of the presence of distant metastases, unlike many other malignancies, because of the relatively long survival after the appearance of distant metastasis. Therefore, the optimal timing for starting TKIs remains unresolved, despite repeated discussions.

Our hospital specializes in the full spectrum of thyroid cancer treatment, from diagnosis and surgery to radioiodine internal therapy and pharmacotherapy. TKI treatment has been given to more than 100 patients so far, with a 2-year survival rate of 51% and progression-free survival of 13.8 months in patients treated with lenvatinib. The factors associated with prognosis have been found to be performance status at treatment initiation, tumor-related symptoms, and tumor diameter. Long-term continuation of each TKI is important to obtain long-term survival due to the high frequency of adverse events and the limited number of available drugs.

In addition to the cancer-specific drugs described above, the number of available drugs that are not restricted to cancer-derived tissues is also expanding. Thyroid cancer is well known to have a relatively high frequency of actionable genes that can access therapeutic targets. Promising target molecules include NTRK, RET, and BRAF. Some drugs such as NTRK inhibitors, RET inhibitors, combination BRAF inhibitors and MEK inhibitors, and combination BRAF inhibitors and immune checkpoint inhibitors are now being developed. The possibility of cure, safe use for advanced cancer patients, and low frequency of side effects are the ideals for anti-cancer drugs. Some reports have shown the safety and efficacy of drugs that meet these conditions.

Furthermore, cancer multi-gene panel testing has been covered by insurance since 2019 in Japan. The testing can be performed in only a limited number of facilities, and only a limited number of patients have access to available drugs based on the testing at the moment. However, greater proliferation of precision medicine is expected in the future as experience accumulates.

The treatment strategy for thyroid cancers involves understanding that the prognosis is good after the appearance of distant metastases and that RAI is available. Therefore, the next issue is when to

consider cancer multi-gene panel testing. There are also unique characteristics of thyroid cancer. For instance, there can be a time delay between the first surgery and when tissue samples for genetic testing need to be obtained, and even when genetic information is actually desired, it is often difficult to sample metastatic lesion sites because of the anatomical features.

Thus, in considering the strategy for thyroid cancer treatment, it will be necessary to find answers to the issues that we face now and in the future.

Discourse

Introduction of the speaker of discourse

Koichi Ito, MD, PhD

Managing Director, IMSJ

We have the honor to invite Mr. Masato Mizuno as a speaker today.

Mr. Mizuno graduated from Konan University's Economics Department and finished Science at Carthage College, Wisconsin, USA. He served as the third president and chairman of Mizuno Corporation, a sports equipment manufacturer. Notably, he spends a lot of time on social services, including sports, the Olympics, the Boy Scouts, and the Rotary Club.

Mr. Mizuno has been a member of the International Olympic Committee in the sections of sports and the environment for 20 years since 1996. He will deliver a lecture about his long-standing research theme.

Discourse: The measures for the SDGs.

Masato MIZUNO

Senior Corporate Adviser

Mizuno Corporation

I would like to talk with you today requested by Dr. Koichi Ito, the director of the Thyroid Disease Hospital and a fellow of the Tokyo Rotary Club. Humankind is in danger of extinction due to climate change caused by global warming. Today's talk is about the United Nations-led SDGs, the Sustainable Development Goals.

Ecosystems on Earth are expected to become extinct in the near future. The United Nations has set 17 items as sustainable development goals from 2015 to 2030 in order to systematize and put into practice what humankind can do to extend extinction as much as possible. We are requesting governments, organizations, and companies in each country to scrutinize what they can do, set numerical targets, and implement them.

From the middle of the 18th century to the 19th

century, mass production due to the Industrial Revolution and convenience of life due to many inventions progressed at an accelerating rate.

The population of the earth at the beginning of the 20th century was 1.6 billion, 100 years later, 6.4 billion at the beginning of the 21st century, the population has quadrupled in the last 100 years, and the world population has continued to grow in the next 20 years, food, water and health. , Medical care, education, energy sources, ecosystems, social systems, etc. While enjoying a very convenient era with advanced scientific civilization, global warming has occurred due to the large amount of carbon dioxide generated by using fossil fuels as an energy source, and the global ecosystem and humankind have become extinct due to major climate change.

Even now, global warming due to the large consumption of fossil fuels has caused remarkable climate change beyond imagination and has become a major threat to the extinction of humankind. The glaciers in the world are disappearing, and the permafrost in Siberia is melting and methane gas, which has a greenhouse effect 23 times that of CO₂, is blowing up from below. Rising sea surface temperatures generate a large amount of water vapor, causing huge typhoons, localized heavy rains, breaking the food chain of marine resources, and drastically reducing fishery resources. American tornadoes have become bigger than ever, and tornado damage has been reported even in Japan, where there were no tornadoes. It causes heavy rains, floods, landslides, and damage to agriculture such as forest fires and droughts.

The United Nations has been holding the United Nations Framework Convention on Climate Change (COP) every year since the Earth Summit in Rio in 1992. I planned the Millennium Goals from 2000 to 2015, but it didn't go as expected. The United Nations is strongly working on the SDGs from 2015 to 2030, as the damage caused by global warming and climate change is becoming more prominent worldwide.

These 17 items

1. Eliminate poverty
2. Zero hunger
3. Health and welfare for all
4. High quality education for everyone
5. Achieve gender equality
6. Safe water and toilets around the world
7. Energy for everyone
8. Both job satisfaction and economic growth
9. Foundation of industry and innovation
10. Eliminate inequalities in people and countries
11. Creating a town where you can continue to live
12. Responsibility to make, responsibility to use
13. Take concrete measures against climate change

14. Protect the abundance of fish
15. Protect the richness of the land
16. Peace and justice for all
17. Achieve goals through partnership

In addition to global warming countermeasures, there are basically a list of measures to live a healthy life. Currently, there are 87 democracies and 92 non-democratic countries on the planet, and there are challenges to be solved such as human rights issues and the gap between rich and poor.

In any case, we must do our best as we are in danger of extinction. It is time for social activities and corporate activities to change from greedy capitalism to public interest ethical capitalism, democratic national governance in which all nations decide soundly by voting by the people, and corporate governance that does not tolerate injustice.

Let's solve many difficult problems with ingenuity and continuity, and cooperate so that the earth can be sustained for as long as one day.

We want to keep planting apple trees cheerfully even when the last day of the earth comes.