

# Medical oncology in Asia

**Kazuo Tamura**

President, the Japanese Society of Medical Oncology

*Corresponding to:* Kazuo Tamura, M.D. The Department of Medicine, Division of Medical Oncology, Hematology and Infectious Diseases, School of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180 Japan. Email: ktamura@fukuoka-u.ac.jp

Submitted Aug 01, 2012. Accepted for publication Aug 27, 2012.

DOI: 10.3978/j.issn.2304-3865.2012.08.06

I would like to congratulate that the Society for Translational Cancer Research (STCR) endorsed by the Chinese Society of Clinical Oncology (CSCO) has launched the official journal 'Chinese Clinical Oncology (CCO). I am greatly honored to join editorial members of CCO who consist of distinguished researchers, teachers and clinicians around the world and have a privilege to write an editorial in the first issue of CCO as an editorial member.

## **Lessons from sorafenib study for hepatocellular carcinoma; a medical oncologist is a must for systemic cancer therapy and to develop a new agent**

There was no standard systemic therapy by using cytotoxic anti-neoplastic agents for hepatocellular carcinoma (HCC) until molecularly targeted agents appeared in the oncology field. Sorafenib is a multi-target tyrosine kinase inhibitor which simultaneously inhibits molecular components of the Raf-MEK-ERK signaling pathways, and VEGFR family and PDGFR-beta leading to abrogating tumor growth as well as neoangiogenesis. It is approved for the use of renal cell carcinoma and Llovet *et al.* for the first time reported usefulness of sorafenib for HCC namely by the SHARP trial (1). Patients with advanced HCC were randomized to receive either sorafenib or placebo. Primary end point was overall survival (OS). Median survival time in the sorafenib arm was 10.7 months (mo), while that of placebo was 7.9 mo ( $P < 0.001$ ), indicating that sorafenib was superior to placebo for treatment of HCC. Same results were observed in the study conducted in patients from Asian-Pacific regions involving China, South Korea and Taiwan with unresectable or metastatic hepatocellular carcinoma (2). Since sorafenib is an anti-neoangiogenic effect in the tumor, it is worth

evaluating sorafenib as an adjuvant after curative or locoregional therapies.

Japanese and South Korean investigators conducted a randomized study between sorafenib and placebo after transarterial chemoembolisation (TACE) for unresectable HCC. Median time to progression (TTP) in sorafenib and placebo groups was 5.4 and 3.7 mo, respectively (hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.70-1.09;  $P = 0.252$ ) (3). Thus, the results were unexpectedly negative to show superiority of sorafenib over placebo. Intent-to-treat exploratory subset analyses were performed in subgroups by hepatitis virus, response to TACE, number of lesions, number of prior courses of TACE, age, sex, treatment lag, ECOG PS and country of enrollment. Although the study was not powered to compare subgroup response to treatment, most HRs in each group showed tendency in favor of sorafenib. Striking differences, however, were seen between Japanese and Korean patients. The HR for TTP was 0.94 (95% CI, 0.75-1.19) for Japanese patients and 0.38 (95% CI, 0.18-0.81) for Korean patients. Japanese patients were 11 years older and had more liver lesions. Older patients might not have tolerated sorafenib and stopped it early. However, the difference in HR for TTP was so large that it could not be explained only by the background difference between the 2 groups. The paper published in the journal did not sufficiently discuss it in detail (3). I talked on this issue with one of the Japanese authors and it appears that most Japanese hepatologists participating in this study were not an oncologist and had not experienced administration of molecularly targeted agents at the time of study. Common side effects of sorafenib such as hand-foot skin reaction (HFSR; 82% of incidence), elevated lipase (44%), alopecia (41%) and rash/desquamation (40%) were not frequently seen in cytotoxic

anti-cancer agents used for HCC and therefore, had not been experienced by the Japanese investigators, while sorafenib rarely showed dramatic shrinkage in tumor size of HCC. It seems to me that these 2 facts made both Japanese patients and investigators unwilling to continue the study when visible adverse events like HFSR developed. Indeed, the median treatment duration was substantially shorter in Japanese than Korean patients (16 versus 31 weeks) despite of no significant difference in adverse events between the 2 groups. Apparently Korean patients were treated with experienced oncologists in Korea. After sorafenib was approved for treatment of advanced HCC in Japan, Japanese hepatologists now are treating HCC patients with the dose and schedule as instructed in the drug label of sorafenib. This study taught us that we need experienced professionals to give anti-neoplastic agents to appropriate patients safely and effectively.

### **Medical oncology is a discipline of systemic cancer therapy and a new field in medicine in Asian countries**

Advances in tumor biology and developing anticancer drugs have produced many useful novel anti-neoplastic agents based on cancer biology, and role of systemic therapy with chemotherapy has become more and more important in treating not only advanced or recurrent cancer but also an early stage of the disease as an adjuvant. In the second part of this editorial, I would like to focus on a professional specialized in systemic cancer therapy.

Medical oncology is a relatively new discipline in the medical field. Physicians who are trained in the field of medical oncology and administer a systemic cancer therapy to the patients are designated as a medical oncologist. Subspecialty in medical oncology was established by the American Board of Internal Medicine (ABIM) back in 1973, and now more than 10,000 ABIM-certified medical oncologists are serving in United States of America. In Europe, the European Society of Medical Oncology (ESMO) started a qualification examination for medical oncology in 1989. Since medical oncology is a new discipline compared with other medical fields such as cardiology, neurology and hematology, it has not been well recognized worldwide not only by medical societies but also by patients, their family and citizens. Indeed, the discipline of medical oncology finally gained the professional qualification in European Union in March, 2011. It is now covered under the European Union Directive. Professor

P. G. Casali, Chair of Public Policy and European Affairs Committee of ESMO celebrated this event by saying 'Medical oncology: the long-awaited prize of recognition' in the editorial of *Annals of Oncology* (4).

Now we turn our eyes on Asian countries. CSCO was established in 1997 (5), while was founded the Korean Association for Clinical Oncology (KACO) in 2005 (6) and the Japanese Society of Medical Oncology (JSMO) in 2002 (7), respectively. CSCO has more than 10,000 individual members (presented by Prof. Jin Li from Fudan University at the leadership meeting with JSMO held in Osaka on July, 2012). Number of qualified medical oncologists must be less than those of individual members in each society. For example, JSMO has 8,500 members and so far 716 physicians have passed a qualification examination of subspecialty in medical oncology. Thus, medical oncology is still a developing new medical field in Asian countries.

I would like to discuss the reasons why medical oncology is necessary. Cancer patients had long been managed by organ-specific physicians, especially surgeons. For example, lung cancer was operated upon by chest surgeons, and after operation, surgeons used to give chemotherapy and ask radiologists to give a radiation therapy to patients if indicated. Surgeons followed up them in the clinic. When patients relapsed, surgeons started second line chemotherapy or best supportive care by themselves. In contrast, internists made a diagnosis of lung cancer, but usually did not treat patients for cancer after patients were transferred to a surgical department. Cancer is a systemic disease except for a very early stage of disease, but surgery and radiation is a treatment modality of local disease. If a patient with lung cancer develops meningitis carcinomatosa, who would primarily take care of the patient? It is quite difficult to find a right specialist who can give an intrathecal administration of anti-cancer agents and appropriate management for metastatic diseases in central nervous system. It is not uncommon to see patients with lung cancer who have second or third malignancies, e.g., head and neck and esophageal cancer. Who is going to treat such a patient having double or triple cancer?

Cancer is a systemic disease except for an early stage of disease. It can infiltrate directly into surrounding tissues which include pleura, peritoneum and meninges, and spread any places in the body via blood and lymphatic channels. Complications are inevitable depending on metastatic sites. For example, peritoneal spread by cancer induces ascites formation associated with symptoms of abdominal fullness and decreased food intake leading to

malnutrition, and metastasis to the brain is accompanied by symptoms of increased intracranial pressure with headache and nausea. Some patients are complicated with paraneoplastic syndromes such as hypercalcemia associated with parathyroid hormone-related protein production by the tumor. In addition, the average age of newly-diagnosed cancer patients is now well over 60 years.

Elderly patients have usually several coexisting chronic medical problems e.g., hypertension, diabetes mellitus and cerebrovascular events. They have also more or less geriatric syndromes of frailty (falls), incontinence and delirium. The psychosocial issues in the aged often give a difficult problem to medical practice. They often live alone or with their old spouse, and their income is mostly limited to a pension. These conditions not uncommonly lead senior cancer patients to be ignored by the family and medical services or to receive inappropriate therapy. Furthermore, advances in cancer medicine have increased not only a cure rate but also a number of patients who are living with cancer resulting in rapid increase in cancer survivors.

When we put all characteristics of cancer described above together, i.e., cancer is a systemic disease, a disease of old age and becoming a chronic disease, we need medical oncologists as a cancer specialist who is responsible for general medical care as well as systemic cancer therapy.

When they are to be trained in medical oncology, a training program must be established based on an adequate curriculum. ESMO and ASCO task force timely published the global curriculum in medical oncology in 2004 (8) and updated it in 2010 (9). Medical and social backgrounds, of course, differ from country to country, and therefore, oncology societies in each country have to make a proper program fit to each country along the line of global curriculum. It covers basic tumor biology, cancer prevention, diagnosis and treatment, palliative care, patient education, bioethics and psychosocial issues, skills, and even cancer care delivery in low resource environments of low and middle income countries. It is indeed 'global' since the curriculum includes essential knowledge and skills to be mastered by medical oncologists of any country.

Medical oncology training requires a minimum of 5 years which include at least 2 years of training in general internal medicine first followed by a minimum of 2 years of training in oncology according to the global curriculum. Oncology training must be carried out under supervision of program leader medical oncologists in institutions where appropriate resources and facilities are available. Trainees should have clinical experience for common cancers such

as breast, gastrointestinal (GI) tract and lung cancer as well as hematological malignancies. After training in medicine and oncology, they are obliged to take a qualification examination and to be certified that they have appropriate knowledge, skills and attitude to take general care of cancer patients and to give at least standard chemotherapy to common cancers. A program director in training institutions can evaluate achievement of the program for trainees by using the Log Book (10).

Advances in cancer medicine have produced anticancer agents targeting specific molecules that are overexpressed in the cells or products of abnormal genes. Thus, cancer medicine moves rapidly towards tailor-made, individualized medicine depending on targeting molecules. In lung, breast and GI tract cancers for example, many molecularly targeted agents have become available. Special attention must be paid on biological markers before the start of treatment and drugs are given to appropriate patients based on the results of biomarker testing. These agents have different toxicity profiles compared with cytotoxic chemotherapeutics and some of them have a risk of fatality. For example, interstitial lung disease induced by tyrosine kinase inhibitors such as gefitinib lead to respiratory failure and death. In this case, it is important to note that incidence of pulmonary toxicity differs between Caucasians and Asians. Ethnic difference in treatment response and adverse events should be considered when new molecularly targeted agents are investigated. Using such drugs requires special experience on top of the knowledge and skills of general oncology. In the era of a targeted therapy, oncologists specialized in cancer of one organ may be needed like a breast medical oncologist and can be assigned to the organ specific clinic. However, such assignment can be possible only after general medical oncologists appear in great numbers in the practice.

To ensure optimal treatment and care for cancer patients, medical oncologists must participate in continuing medical education programs. New information derived from results of translational research and clinical study comes out virtually every day. Since they are reported in the literature after presented in a oncology annual meeting like ASCO or ESMO every year, oncologists must catch them up to apply to the patients. Advances in oncology fields are so rapid that recertification examination is needed preferably every 5 years.

In clinical practice, cancer therapy is given by a team consisting of surgical, radiation and medical oncologists, nurses, pharmacists and other health-care providers. Medical oncologists certainly play a pivotal role in making an effective team to provide comprehensive treatment

to cancer patients. Other important role of medical oncologists is to educate young physicians and health care professionals and to establish new evidence of cancer treatment by participating in clinical trials. The latter is one of the important tasks for medical oncologists to develop new evidence in cancer therapy as discussed in the process of developing sorafenib for HCC and keep themselves on the cutting edge of new research development.

There are a wide variety of nations in Asian-Pacific regions from developing to industrialized countries. Medical oncology has not been spread over these areas yet. All patients from any countries have a right to receive at least a standard therapy for their diseases. Same is true for cancer. However, it takes years for developing nations to gain sufficient resources for supplying standard care to the patients. One thing that academe can do is mutual international collaboration among oncology societies to share the goal of our mission, educate cancer professionals and health-care providers, and conduct international clinical trials to develop a better therapy. Through that process we also raise an able medical oncologist who can work internationally. One of the proposed is an exchange program for young physicians between the societies. They can learn a different set of cancer and cancer medicine by being exposed to practice, education and research in the visiting country, since epidemiology and treatment resources differ from country to country.

An international session in the annual meeting of each society is also worth taking place. Hot discussion by international attendees will improve knowledge and way of thinking in cancer medicine as a medical oncologist. It is time to strengthen ties through bidirectional exchange and collaboration between cancer societies especially around Asian-Pacific regions. This can lead us to achieve our final goal, i.e., recognition of medical oncology in the national and international medical societies and people in the world. It takes time, but by working together, we should be able to have a sufficient number of well-trained medical oncologists as well as health-care professionals.

After all is proposed and done, medical oncologists can achieve career success in oncology and above all,

it guarantees, I believe, that all cancer patients are to be treated by a qualified and well trained professional workforce and best treatment outcome can be achieved in any country of the world.

## Acknowledgements

*Disclosure:* The author declares no conflict of interest.

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**Cite this article as:** Tamura K. Medical oncology in Asia. *Chin Clin Oncol* 2012;1:2. DOI: 10.3978/j.issn.2304-3865.2012.08.06