MEETING REPORT

Japanese Cancer Association Meeting UICC International Session - What is Cost-effectiveness in Cancer Treatment?

Hideyuki Akaza[1]*, Norie Kawahara[1], Jae Kyung Roh[2], Hajime Inoue[3], Eun-Cheol Park[4,5], Kwang-Sig Lee[4,5], Sukyeong Kim[6], Jasdeep Hayre[7], Bhash Naidoo[7], Thomas Wilkinson[7], Takashi Fukuda[8], Woo Ick Jang[9], Masafumi Nogimori[10]

Abstract

The Japan National Committee for the Union for International Cancer Control (UICC) and UICC-Asia Regional Office (ARO) organized an international session as part of the official program of the 72nd Annual Meeting of the Japanese Cancer Association to discuss the topic "What is cost-effectiveness in cancer treatment?" Healthcare economics are an international concern and a key issue for the UICC. The presenters and participants discussed the question of how limited medical resources can be best used to support life, which is a question that applies to both developing and industrialized countries, given that cancer treatment is putting medical systems under increasing strain. The emergence of advanced yet hugely expensive drugs has prompted discussion on methodologies for Health Technology Assessment (HTA) that seek to quantify cost and effect. The session benefited from the participation of various stakeholders, including representatives of industry, government and academia and three speakers from the Republic of Korea, an Asian country where discussion on HTA methodologies is already advanced. In addition, the session was joined by a representative of National Institute for Health and Care Excellence (NICE) of the United Kingdom, which has pioneered the concept of cost-effectiveness in a medical context. The aim of the session was to advance and deepen understanding of the issue of cost-effectiveness as viewed from medical care systems in different regions.

Keywords: UICC-ARO - JCA meeting - cost-effectiveness - cancer treatment - guidelines

Asian Pac J Cancer Prev, **15 (1)**, 3-10

Introduction

UICC is a membership organization that exists to help the global health community accelerate the fight against cancer. Founded in 1933 and based in Geneva, UICC's growing membership of over 760 organizations across 155 countries, features the world's major cancer societies, ministries of health, research institutes and patient groups. Together with its members, key partners, the World Health Organization, World Economic Forum and others, UICC is tackling the growing cancer crisis on a global scale.

As part of the official program of the 72nd Annual Meeting of the Japanese Cancer Association the Japan National Committee for UICC and UICC-Asia Regional Office (ARO) organized an international session to discuss the topic "What is cost-effectiveness in cancer treatment?" Presenters and participants discussed the question of how limited medical resources can be best used to support life, which is a question that applies to both developing and industrialized countries, given that cancer treatment is putting medical systems under increasing strain. The emergence of advanced yet hugely expensive drugs has prompted discussion on methodologies for Health Technology Assessments (HTA) that seek to quantify cost and effect. The session benefited from the participation of various stakeholders, including representatives of industry, government and academia and three speakers from the Republic of Korea, an Asian country where discussion on HTA methodologies is already advanced.

In addition, the session was joined by a representative of National Institute for Health and Care Excellence (NICE) of the UK. The aim was to advance and deepen understanding of the issue of cost-effectiveness as viewed from medical care systems in different regions. The session was co-chaired by Hideyuki Akaza, Research Center for Advanced Science and Technology, The University of Tokyo, Japan, and Jae Kyung Roh, Yonsei Cancer Center, Yonsei University Medical School, Republic of Korea.

*[1]Department of Strategic Investigation on Comprehensive Cancer Network, Research Center for Advanced Science and Technology, University of Tokyo, [3]Ministry of Health, Labour and Welfare, [8]National Institute of Public Health, Japan, [2]Yonsei Cancer Center, [4]Department of Preventive Medicine, Yonsei University, Republic of Korea; 5Institute of Health Services Research, Yonsei University, [6]Research Department, Health Insurance Review and Assessment Service, [9]R&D Division, Republic of Korea; 7National Institute for Health and Care Excellence (NICE), United Kingdom, [10]Astellas Pharma Inc. *Email: akazah@med.rcast.u-tokyo.ac.jp*

Opening Remarks

Hideyuki Akaza (RCAST) welcomed participants to the UICC International Session, entitled "What is cost-effectiveness in cancer treatment?" The session was being hosted by the UICC Japan Office and UICC-Asia Regional Office (ARO) (Akaza, 2013). He began by noting the great cost involved in developing new anti-cancer drugs and the problems this is creating all around the world. He explained that the first three presentations would present perspectives on cost-effectiveness from the government and administrative side, following which two presentations would discuss cost-effectiveness from an academic perspective. Finally, the issue of cost-effectiveness would be presented from the viewpoint of pharmaceutical companies. Following the presentations there would be time for general discussion. Jae Kyung Roh (Yonsei University), acting as co-chair with Hideyuki Akaza also welcomed participants.

1. Recent Discussion on Cost-effectiveness at the Health Ministry's Council

Hajime Inoue (Ministry of Health, Labour and Welfare (MHLW)) noted that in many areas of cancer treatment, the introduction of new tracks of drugs completely changes the way patients are treated. One of the key factors is the fair evaluation of new medicine. He reported on the recent considerations with regard to cost-effectiveness at the MHLW ministry council.

In Japan the prices of all prescription medicines are priced at the Central Social Insurance Medical Council ("Chuikyo"). All cancer drugs are promptly covered, priced and made accessible to all. Pricing is based on "added value" compared to existing analogous drugs, or on "cost accounting" methods if no analogous drugs exist. Price adjustment is based on the foreign price of the drugs in question. Until recently Hajime Inoue had served as the secretary of the Chuikyo council meeting. The pricing of new medicine is one of the highest concerns for all stakeholders involved. Many people are not completely satisfied with the current pricing mechanism, which is considered to be overly vague and does not reflect the current situation with medical innovation. In February 2012 Chuikyo made a resolution to request the MHLW minister to examine the feasibility of evaluating the cost effectiveness of new technologies, including new cancer drugs.

Since May 2012 the Chuikyo Subcommittee on Cost-Effectiveness Analysis has met on 13 occasions and a provisional draft report was issued in September 2013. Points of issue include cost, effectiveness and application, although subcommittee members have yet to reach a decision on how to define cost, how to measure effectiveness, and how to apply cost-effectiveness analysis into the pricing system. There are two major concerns that underlie the technical discussions in this subcommittee, namely how does cost-effectiveness affect price of and access to new drugs.

With regard to pricing, the concern is that if cost-effectiveness is another word for price containment, there are precedents in other countries where new drugs have been contained. On the other hand, cost-effectiveness could be viewed as simply differentiating real innovation from mediocre efforts, and pricing accordingly.

With regard to access, there are concerns that cost-effectiveness analysis could hinder access if coverage is restricted, as has been the case in other countries. On the other hand, it could be viewed that cost-effectiveness analysis is simply a method to redistribute finite resources for more effective use.

In the ongoing discussions at the Chuikyo ministry council further considerations will be required in order to reach convergence. It is necessary to devise an objective, reliable index (or combination of indices) to measure effectiveness in a Japanese context. Quality Adjusted Life Years (QALY) is one method of measuring cost-effectiveness, but it is insufficient on its own. Another concern of the MHLW ministry council is to identify real innovation and price accordingly, thereby rewarding innovation and not containing it. Another issue is to discuss the ways in restriction on drugs could be accepted in the case of "less-effective" use.

2. Cost Effectiveness of Cancer Treatment in Korea

Eun-Cheol Park (Yonsei University) noted that his presentation would include three parts: the burden of cancer in Korea, cost-effectiveness analysis (CEA) for cancers and conclusions. Annual cancer incidence and mortality rates are increasing rapidly in Korea, with the cumulative risk of cancer standing at 37.6% for males and 33.3% for females (as of 2010). Cancer accounts for 27.8% of all deaths in Korea (as of 2012). The economic burden of cancer has been estimated at US$24.1 billion. Disability adjusted life years (DALY) are expected to continue to increase for almost all cancers.

With regard to CEA, the first question to ask is if prevention better than cure. If incremental effectiveness exceeds the incremental cost, then it can be considered that prevention is better than cure. Cost-effectiveness can be measured in terms of life years saved, QALY and direct/indirect benefits. In monetary terms it is possible to consider a human capital approach and also a willingness to pay. The dimensions of cancer control include prevention, early detection, diagnosis and treatment, and palliative care. Contributing factors such as smoking, alcohol consumption, infection and obesity all can be controlled to reduce the likelihood of contracting cancer. In terms of CEA results, one study showed that the eradication of helicobacter pylori in gastric cancer survivors after endoscopic resection of early gastric cancer reduced overall costs by US$814 and resulted in LYS of 0.05 years.

Early detection is also very important and in Korea the National Cancer Screening Program (NCSP) has been in operation since 1999. Screening for various types of cancer, including stomach, liver, colorectal, breast and cervical cancers, are implemented regularly for the entire population in certain age groups. However, CEA in Korea has shown that for some cancers, including breast

cancer, treatment is cost-effective in Western countries, but not cost-effective in Asian countries. There is also divergence in the quality of care provided, depending on the geographic location of the hospital providing care.

In Korea efforts are being made to engage in primary prevention efforts for the most prevalent forms of cancer, including stomach, liver, colorectal and lung cancers. Efforts include anti-smoking campaigns and information about how to reduce salt intake. Early detection is another area that is being increasingly focused on. Palliative care efforts include the expansion of hospices and the creation of models for acute palliative care.

More evidence is required concerning methods for reducing the burden of cancer, including effectiveness and cost-effectiveness evidence.

3. Current Decision-making of Natl Health Insurance on Anti-cancer Drugs in Korea

Sukyeong Kim (Health Insurance Review and Assessment Service (HIRA)) began by explaining about the introduction of a positive list system in Korea. She noted that a high proportion of pharmaceutical expenditure has always been a big burden in national health expenditure in Korea, at a higher than average level in comparison to other Organization for Economic Co-operation and Development (OECD) countries (24-25% vs. 17-18%). In terms of the National Health Insurance (NHI) pharmaceutical expenditure, the annual growth rate was 14.6% between 2001 and 2005, with pharmaceuticals accounting for 29% of all NHI spending in 2005. The increases can be explained by an aging population and an increase in chronic diseases and the early adoption of new drugs and wide NHI coverage of pharmaceuticals. The government of Korea announced a Pharmaceutical Expenditure Reconciliation Plan in May 2006, following by the adoption of the positive list system in December 2006.

Under the positive list system selective reimbursement for new drugs is based on cost effectiveness in addition to clinical usefulness. Furthermore, decisions on reimbursement and decisions on pricing of new drugs have been split into two. The reimbursement assessment is implemented by HIRA, while price negotiation is undertaken between the National Health Insurance Service (NHIS) and the manufacturer. The system is subject to review, with drugs being delisted if they have not been produced or subject to a claim for two years or more, and reevaluation also being implemented on reimbursement status and price.

Before the positive list system was introduced almost all drugs were covered by the NHI system. Following the introduction, only drugs with clinical and economic value are covered. A Drug Benefit Assessment Committee (DBAC) comprising 21 specialists from various stakeholders, including companies, consumers and government agencies assess drug appropriateness and recommend reimbursement. There is also an Anticancer Drugs Review Committee under the DBAC that advises and controls the off-label use of anti-cancer drugs. The DBAC considers "essential drugs" to be those that fulfill the following criteria: No alternative treatments and drugs; use for severe, life-threatening diseases; use for a minority of patients who have rare diseases etc.; and drugs that are proven to provide clinically meaningful improvement for patients. NHIS negotiates drug price and its expected volume with the company after a decision has been made by the DBAC.

In terms of the evaluation of the positive list system, the average recommendation rate from 2009 to 2012 was 73%. A total of 92% of recommended drugs satisfied all decision criteria and 59% of rejected drugs demonstrated unacceptable cost-effectiveness. Comparisons with cases in Australia and Canada have shown that there is no evidence to suggest that Korea is more conservative in its recommendation procedures than the two abovementioned countries, with similar decisions forthcoming from all three countries in terms of clinical usefulness, although there were differences in cost-effectiveness assessments. With regard to NHI coverage decisions on anti-cancer drugs, the recommendation rate is almost the same as common drugs. In comparison with the Common Drug Review (CDR) of Canada and NICE UK, recommendation rates are similar for anti-cancer drugs. Off-label use of anti-cancer drugs is reviewed by an expert committee. Government policy in Korea is to expand coverage to 100% for anti-cancer drugs, although decisions have yet to be reached on a number of new drugs, or they have already been rejected. Policies will also need to be formulated in the future to respond to ultra-high cost drugs and rare diseases. A special mechanism also needs to be devised that incorporates end of life treatment (including a weighting for QALY), utilization monitoring and assessment of off-label use of anti-cancer drugs.

4. NICE Methods to Assess Cost-Effectiveness of Cancer Treatments in England

Jasdeep Hayre (National Institute for Health and Care Excellence (NICE)) began with an explanation about the background to NICE. The United Kingdom (UK) has an entirely taxpayer-funded system with no public health insurance scheme and results in fixed budgets with scarce resources in the health service. In the 1990s, local commissioners and providers at the local level would make decisions about what was made available to local populations. This system led to a so-called "postcode lottery" for patients, where treatment would differ depending on geographic location. There was public and political dissatisfaction with the availability of treatments. NICE was formed in 1999 and is based on four principles that underpin all NICE guidance: 1) based on the best available evidence, 2) maximize clinical and cost effectiveness, 3) developed systematically and transparently, and 4) developed with stakeholder engagement. From 1 March 2000 to 31 August 2013 NICE has looked at over 500 treatments, over 130 of which have been for cancer. Over 170 guidelines have been issued, over 10 of which have been for cancer.

With regard to cost effectiveness issues, NICE's aim is to maximize health benefit given budget constraints. What NICE is interested in is comparative or incremental

differences between drugs, namely is the extra health gain from a certain new drug worth the extra money spent? In order to measure the health gain, NICE uses Quality Adjusted Life Years (QALY). QALYs combine both quantity and health-related quality of life (QoL) into a single measure of health gain. The amount of time spent in a health state is weighted by the QoL score attached to that health state. The benefit of the QALY is that it can weigh up the net effect of treatment for patients, including survival vs. QoL, long-term QoL for chronic and recurrent conditions, and benefits vs. harms.

In terms of economic evaluation and decision making, NICE uses the incremental cost effectiveness ratio (ICER), which gives the cost per one QALY gained. If the ICER is above £20,000 to £30,000 per QALY gained, a stronger case is needed to recommend the drug.

In terms of the appraisal process, under a single technology appraisal process a company generally submits a new drug for assessment by an external review group. The appraisal committee then produces draft advice to approve, reject or restrict access to the drug, with comments also being received from stakeholders, after which guidance is issued. An appeal process is also incorporated. There are different processes for all other NICE guidance (including guidelines, diagnostics, and interventional procedures). However, there are further "special circumstances" that also need to be taken into consideration. The application of "special circumstances" in the appraisal of some products with ICERs above £30,000 per QALY has been seen in a number of cancer drugs. Several special circumstances have been applied in the past, including consideration of "severity," "end-of-life," "stakeholder persuasion," "significant innovation," "disadvantaged populations" and "children." (Rawlins et al.,, 2010).

Most relevant to cancer are the "end-of-life" criteria. Additional consideration can be given for treatments which affect people at the end of their life (usually with cancer). End-of-life criteria can be applied if the following conditions are met: the treatment is indicated for patients with a short life expectancy, normally less than 24 months, and there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current National Health Service treatment, and the technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7,000 for all licensed indications in England.

Looking at both economic considerations and special circumstances, NICE has approved approximately 58% cancer drug indications (63% for non-cancer drug indications) or optimized 4% of cancer drug indications (17% for non-cancer drug indications), which is broadly in line with international trends although a little more conservative than approval processes in seen in Asia. There may be a political and social argument for accepting more cancer drugs and the question of whether cancer treatments should have a higher ICER threshold (greater than £30,000 per QALY) is one that is still being discussed. There is no significant academic evidence to show that cancer drugs should be given a higher acceptance threshold than for other drugs.

With regard to the Cancer Drugs Fund, this scheme was introduced by the Department of Health in April 2011 to "enable patients to access the cancer drugs their doctors think will help them." Additional government funding (£200 million) has been provided to pay for drug / indication combinations appraised by NICE and not recommended on the basis of cost effectiveness, or where the recommendations materially restrict access to the treatment to a smaller group of patients than the specifications set out in the marketing authorization (an 'optimized' recommendation), and drug / indication combinations on which NICE has not, or not yet, issued appraisal guidance. Very recently a further £400 million was provided for the fund, which will ensure funding up to March 2016. The fund covers around 31 drugs (108 indications) and in one quarter there were almost 5,000 prescriptions. The most popular drugs prescribed under the fund are bevacizumab and abiraterone. The most prescribed indication for bevacizumab using the fund was for an indication NICE had rejected. The most prescribed indication for abiraterone using the fund was for one which had not been appraised by NICE.

In summary, NICE provides a robust and transparent system to assess all treatments, including cancer treatments and interventions for a fixed budget system. Some special circumstances can be considered. Although this system may not be a perfect solution it does approve approximately 64% of anti-cancer indications. There is some political willingness to go further and perhaps give cancer drugs more "weight" or funding, through the Cancer Drugs Fund.

5. Cost-effectiveness Analyses and Cancer Treatment in Japan

Takashi Fukuda (National Institute of Public Health) noted that in Japan a public health insurance scheme covers the whole population, however, there are about 3,000 health insurance bodies. People in Japan have to join one of the health insurance bodies. In 2010, annual medical expenditure was around 37 trillion yen, which is approximately 7.8% of gross domestic product (GDP). Medical expenditure continues to increase by approximately 1 trillion yen each year. One of the reasons for the increase in medical expenditure is population aging. Elderly people account for approximately 23% of the total population. Another significant reason is the ongoing advancement of technologies in health care and new drugs. Cancer accounts for a large proportion of medical expenditure (approximately 3.5 trillion yen in 2010).

Even though medical expenditure of cancer is increasing, the economic burden to society may be decreasing, because of decreased mortality at younger ages. However, increased medical expenditure must be borne by health care finance. Especially in recent years, expensive drugs and treatments have appeared and they may cost a great deal of money. The question this presents is: should we avoid expensive drugs and treatment because of large expenditure?

The issue of harmonizing advancing technology and expenditure is a difficult one to address. It is difficult to increase taxation, insurance premiums and patients' out-of-pocket payments due to the current economic climate in Japan. It would also be difficult to limit the extent of insurance coverage, as all prescription drugs are covered by the national health insurance scheme. There are also questions about whether to implement price or volume controls, but this could cause inequality in the system.

One example of cost-effectiveness analysis of a molecular-targeting drug is adjuvant trastuzumab. After 2005, several randomized control trials (RCTs) have confirmed the usefulness of trastuzumab as adjuvant therapy for HER2-positive patients, not only as metastatic therapy. However, the costs of one year of treatment are approximately 3.2 million yen. Adjuvant trastuzumab is "revolutionary" treatment but the costs are not low. Although initial costs are high it is highly possible that adjuvant trastuzumab treatment may reduce the medical costs of recurrence or metastatic breast cancer patients. The objective of this study was to evaluate efficiency by performing cost-effectiveness analysis of adjuvant trastuzumab treatment compared with observation alone. Cost-effectiveness analysis was implemented with an outcome measure of life-years gained (LYG). Efficacy data was based on the 2-year HERA interim analysis in 2007. Only direct medical costs were estimated based on the Japanese drug tariff and reimbursement schedule in 2004, not including indirect costs. It is unknown how long the effect of trastuzumab continues. The cost-effectiveness of trastuzumab was calculated for three hypothetic scenarios, with risk reduction continuing constantly for two years, five years, and ten years. The recurrence risk after five years was assumed to be half that of the previous five years, continuing for the patients' lifetime by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis. The period of trastuzumab efficacy was the most influential parameter on the result of cost-effectiveness. However, when trastuzumab efficacy continues for more than two years, at least, which is a conservative setting judging from the joint analysis (NSABP B-31 and NCCTG N9831 trials), the ICER is less than JPY 7,500,000 for any patient weight class.

NICE suggests that the ICER threshold should be £20,000 to £30,000 (=3,000,000 to 5,000,000 yen) per QALY, however, in Japan, 5,000,000 to 6,000,000 yen per QALY is often referred to as a benchmark, based on a willingness-to-pay (WTP) study.

In the trastuzumab study, the outcome measure was not QALY, but LYG. However, as the therapy mainly prolongs progression-free survival, patient QoL during the period would be not so bad. It was therefore concluded that the therapy was cost effective.

In terms of budget impact, the study considered the incremental cost of 1-year trastuzumab treatment as 2,000,000 to 4,000,000 yen. Then, by estimating the number of new breast cancer patients per year to be 40,000, of which 20% are HER2-positive, the total incremental cost was calculated as 16 to 32 billion yen, if all the HER2-positive patients were treated using trastuzumab.

In summary, it is evident that economic evaluation will be needed to consider appropriate resource allocation under limited public funds for health care.

6. Values and Rewards of Innovative Cancer Drugs: Opportunities for R&D

Woo Ick Jang (Handok) delivered a presentation from both medical oncology and industry perspectives. Cancer is increasingly becoming a chronic disease and targeted cancer drugs are being used more and more either as a single or combination therapy. Cancer treatment is therefore complex and expensive. Most targeted agents are equally expensive regardless of their value. There is a great deal of debate on cancer drug valuation mechanisms and a question that has recently been asked is whether the maximum tolerated price has been reached? The answer is very likely "yes," but various action is being implemented on the part of oncologists and academia.

Chronic myeloid leukemia (CML) experts have recently published a paper entitled "Price of drugs for CML, reflection of the unsustainable cancer drug prices: perspective of CML experts." This study showed price disparities by country and region for the major drugs used to treat CML.

At the academic society level, the American Society of Clinical Oncology (ASCO) Guidance Statement on the Cost of Cancer Care was issued in 2009, which provides a concise overview of the economic issued facing stakeholders in the cancer community. The statement recommends patient-physician discussion about the costs of care.

The United States government implements comparative effectiveness research (CER) in order to compare health care services in a head-to-head manner. CER focuses on results obtained in the real world of typical patients and clinicians. The ultimate goal is to empower the government and private insurers to reduce healthcare costs by restricting access to expensive new medical tests and treatments.

Even in such an environment it is important for the pharmaceutical industry to listen to the opinions of key stakeholders, given the need to consider the payer's perspective from the beginning of drug research and development.

There are a number of case studies available that demonstrate a new approach for cancer drug development and there may be opportunities for R&D in Asia. These include drug development focusing on Asia-prevalent cancers and reducing development costs by shortening drug development time by rapid patient enrollment, as well as risk sharing using government funding, and collaboration with Asian cooperative study groups.

Currently not many first-in-class innovative products are produced in Asia and they are considered to be high-risk. More precise biomarker-driven drug development targeting sub-populations could be expected to have higher efficacy and better safety and have longer treatment duration. Beside first-in-class drug development, some Asian pharmaceutical companies tried to develop fast follow-on products aiming already known cancer targets

with relatively small development cost by accelerating product development. These products were approved by local regulatory authorities by accepting relatively simple studydesign.

The first case study is that of Icotinib, a new lung cancer drug in China. This oral EGFR TKI (TID) was approved in 2011 in China only. The product was developed by Zhejiang Beta Pharma and was partly supported by grants from the Chinese National Key Special Program for Innovative Drugs. Phase 3 trial was completed quickly by rapid patients enrolment and by using PFS as primary efficacy endpoint.

The second case study is that of Radotinib, a new CML drug in Korea. The drug was approved as second line treatment in 2012, which has overall good efficacy and safety. It was developed by Il-Yang Pharm and partly supported by the government. These two cancer drugs show the possibility for domestic company to develop new cancer drugs quickly and cheaply, eventually providing better cost-effectiveness drug to the patients.

In conclusion, many questions remain concerning the values and rewards of new targeted cancer drugs, and stakeholder voices and opinions are increasing on this issue. An alternative development approach is required in order to reduce the price of cancer drugs.

7. Anti-cancer Drugs: Innovation and Improvement of Access

Masafumi Nogimori (Astellas Pharma Inc.) spoke about some approaches from the pharmaceutical industry to improve innovation and access to drugs. In advanced countries, cancer has become the number one cause of death, but on a global basis the number one cause of death is derived from cardiovascular diseases, including ischemic heart failure and stroke. Cardiovascular, cancer, diabetes, and chronic respiratory diseases are collectively known as non-communicable diseases (NCDs). According to WHO, more than 60% of all 57 million deaths worldwide were derived from NCDs in 2008 and this proportion is expected to reach 76% in 2030. In addition, the proportion of NCD deaths under the age of 60 in low and middle income countries is more than twice that of high income countries. It can be seen that NCDs therefore need to be given serious consideration.

Over the last decade there have been significant innovations in cancer diagnosis and treatments. These include anti-angiogenic drugs, appropriate diagnostic devices, and cancer vaccinations, which have led us to a new era of cancer treatment. However, there are still unmet medical needs.

The pharmaceutical industry has 1,500 new drug candidates in the pipeline to treat NCDs, more than half of which are anti-cancer drugs. Research and development in this area has tried to identify a suitable biomarker that can be used to diagnose and monitor the disease in large patient populations. Many companies are using imaging and computational technologies to address the underlying mechanisms of cancers. This has led to several biotherapeutic advances in treating cancer. In fact, some cancers may be managed as chronic diseases. However, cancer remains one of the world's largest healthcare challenges, with an estimated 12 million deaths annually expected by 2030.

Taking the example of typical molecular targeted drug clinical data for non-small cell lung cancer, Tarceva and Iressa are EGFR-tyrosine kinase inhibitors and have been shown to be more effective in patients with EGFR mutation. Their response rates are higher, and the progression free survival (PFS) time is found to be significantly longer compared with traditional chemotherapies. These new drugs give patients new efficient options to fight cancer, however, the targeted patient population is significantly smaller that for chemotherapies.

The average cost of developing one new medicine has increased dramatically in recent years. Bringing a medicine to market in the early 2000s cost approximately US$1.2 billion, compared to approximately US$140 million in the mid-1970s. One reason for the higher cost of R&D is the increase in the pharmaceutical R&D failure rate. This is because the R&D focus has been shifting to more challenging and difficult diseases. During the last decade, clinical trial designs and procedures have become much more complex, demanding more staff time and effort, and discouraging patient enrollment and retention. Therefore clinical trials have become lengthy and more costly. Although molecular targeted drugs give patients important benefits such as increasing success rates and fewer side effects, they are also costly. We need to seek better ways to tackle this issue globally.

When we look at high unmet medical needs in oncology, a sustainable improvement of health care must be accomplished. When we have efficacious innovative drugs we must also consider how to deliver the drugs appropriately and utilize healthcare systems optimally, for example.

In order to achieve sustainable global healthcare improvement, multi-sectoral cooperation among all stakeholders is imperative. Government, industry, academia and civil society need to work together to make healthcare systems sustainable and to improve access to healthcare beyond drug price issues. For instance, process innovation for the drug development / approval from regulatory science could be considered globally via academia, government, and the industry dialogue. Multi-sectoral innovative cooperation is essential in order to continue to create new medicines and diagnostics and to contribute to improved access to medicine and care.

8. Discussion

Hideyuki Akaza (RCAST) asked Norie Kawahara (Chair of the Asia Cancer Forum) to make comments on the presentations. Norie Kawahara noted that the presentations had been most impressive and that they had shown that the importance of cost effectiveness cannot be underestimated. Without innovation medical service cannot be improved and new innovation has been the outcome of cancer research to date. It is now imperative to consider the meaning of innovation in response to the social agenda.

Tomoyuki Kitagawa (Japanese Foundation for Cancer

presentation by Masafumi Nogimori and his focus on multi-sectoral cooperation in order to respond to soaring medical costs. The hospital visit rate among the Japanese population is much higher than other developed nations and Japanese medical institutions are using expensive medicines luxuariously. It is important to ensure that medicines and treatment are used to the best effect. In Japan it will be important to attempt to change the behavior of the public so that they act more reasonably with regard to doctor/hospital visits. One of the reasons behind soaring medical costs in Japan is the aging population. In the future it might be necessary to encourage voluntary efforts of extremely aged people who refuse to get terminal life-prolonging maneuvers and also sophisticated/expensive treatment with only marginal effect, in order to lessen the burden on national health systems and the younger generation.

Kazuo Tajima (UICC-Asia Regional Office) noted that the UICC Session had started in 2011, and at the inaugural session discussions focused on how to reduce costs. Since then discussions have shifted towards the issue of cost effectiveness. One way of reducing cost and boosting cost effectiveness would be to simplify clinical trials. Quality of life is an important criterion to consider when appraising cost effectiveness. The UICC seeks to promote equitable cancer treatment in developing and developed countries; however, costs can be prohibitive. It is important to develop guidelines for cancer treatment that can be adapted to deal with the actual situation on the ground.

Brian Berry (University of Tokyo) noted that he had found the presentations most insightful and the criteria used for assessing cost effectiveness had been new to him and would likely be new to many people. He suggested that it would be useful to consider ways to educate people about the cost-effectiveness appraisal process in the future, as a way of enlightening the public.

Keishi Yoshida (University of Tokyo) noted that the presentations had inspired him to concentrate on the patients in front of him when he became a medical doctor in the future. He noted that he had found the explanations about cost-effectiveness analysis most enlightening.

Jae Kyung Roh (Yonsei University) invited comments and questions from the floor.

Hiroshi Maeda (Sojo University, Kumamoto) noted that the Japanese national health system is unsustainable in its current state. The issue of medical cost containment is currently also a major issue in the United States. New and costly drugs are covered by medical insurance in Japan and this leads to people not giving thought to the cost of the drugs they are prescribed. He urged that the Japanese government consider the establishment of an independent body, such as NICE, that would deal with cost-effectiveness analysis.

Hajime Inoue (MHLW) responded that the UK National Health Service and the Japanese healthcare system are different in several ways. The UK is entirely taxpayer funded, whereas the Japanese healthcare system is a combination of health insurance premiums, taxpayer funds and out-of-pocket expenses. With regard to out-of-pocket expenses, in the case of the UK approximately 10% of the population are members of additional private insurance schemes, allowing them access to drugs that NICE does not approve. The question is whether such a system would be viewed as being socially acceptable in Japan, where there is a strong focus on equality in healthcare.

Jasdeep Hayre (NICE) added a point of clarification about the implementation of guidance at NICE. It is the case that if NICE issues guidance on the use of a certain drug, every healthcare authority in the country has to make funding available for that drug normally within three months. However, clinical guidelines and other guidance produced by NICE is not legally binding. The UK has a unique healthcare system in that it is almost entirely taxpayer-funded. This is a part of the social values of the UK, where the focus is on healthcare being provided free of charge, but perhaps at the expense of a certain degree of patient choice.

Sukyeong Kim (HIRA) noted that in Korea the public contribution is as big as 85% of the national health insurance funding, with only 15% coming from government. The rapid increase in expenditure is an issue that needs tackling urgently and international cooperation will be required. There are many efforts around the world being implemented to ensure cost effectiveness in the healthcare field and sharing and reviewing these experiences would be useful for all countries. The positive list system in Korea was introduced to ensure that only cost-effective drugs are prescribed. In the initial stage of the positive list system there were complaints from companies about the lack of data available. Increased data would help the public to understand about the effectiveness and cost of the drugs they are using.

Hideyuki Akaza (RCAST) suggested that it would be important to consider changing the way in which R&D of anti-cancer drugs is implemented and in so doing reduce associated costs.

Takashi Fukuda (National Institute of Public Health) agreed with Sukyeong Kim that further international cooperation on cost-effectiveness analysis would be very useful, but noted that global trials of pipeline drugs are already being implemented.

Eun-Cheol Park (Yonsei University) noted that to reduce the development costs of new anti-cancer drugs, we have two strategies. The first strategy as proposed by Woo Ick Jang,is government-driven anti-cancer drug development that the role of government is control tower in early phase of clinical trial and funding source. The second strategy as proposed by Masafumi Nogimori, is high and multi-disciplinary cooperation with public and private partnership.

Jasdeep Hayre (NICE) noted that there is the additional cost of the Health Technology Assessment (HTA) process, which is quite expensive. There is an initiative underway in Europe to streamline the HTA process through international cooperation to create standardized models (EUnetHTA). In terms of the evidence base, instead of having many head-to-head trials, it is possible to use other statistical methods such as network meta-analysis, which can be used to calculate the incremental effect in the absence of comprehensive head to head evidence.

However, less expenditure in data collection, lower quantity or quality of evidence may increase uncertainty estimating the drug's effectiveness making it difficult for decision makers to give strong guidance.

Masafumi Nogimori (Astellas Pharma Inc.) noted that in order to streamline total development cost a unified worldwide development and approval system would be ideal. However, taking a programmatic line, a mutual approval system could also be another option. To combine the wisdom of people must be essential.

Woo Ick Jang (Handok) noted that he had already referred to two cases where development costs had been kept to a low level, in the cases of Icotinib and Radotinib. Only phase II data was required for approval for Radotinib approval. In Korea, there are two funding mechanisms for drug development funded by government, such as National OncoVenture, specialized for cancer development, and the Korea Drug Development Fund for all therapeutic areas. Review committee members comprise many people who have overseas experience and are able to bring their expertise to the process of developing and gaining approval for new drugs. We need to do active collaboration between industry, regulatory agencies and other stakeholders to develop more cost-effective drugs.

9. Closing Remarks

Jae Kyung Roh (Yonsei University) thanked all the presenters for their valuable inputs and thanked the UICC-ARO for its support. He expressed his appreciation to Norie Kawahara for organizing the UICC session and closed the proceedings.

References

Akaza H (2013) Challenges and outlook for the UICC-Asian Regional Office. *Asian Pac J Cancer Prev*, **14**, 4935-37.

Rawlins M, Barnett D, Stevens A (2010). Pharmacoeconomics: NICE's approach to decision-making. *Br J Clin Pharmacol*, **70**, 346-9.