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MEETING REPORT

Meeting report: Current cancer perspectives from the 9th Annual Meeting of the Japanese Society of Medical Oncology

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Abstract

The purposes of Annual Meeting of the Japanese Society of Medical Oncology (JSMO) are to provide a scientific forum among scientists and oncologist, and to bridge research findings from the molecular to clinical application. Cancer treatments can immediately benefit from all areas of oncology: the discovery and clinical application of biomarkers; development of more personalized anticancer therapy including molecular targeted agents; recent findings from clinical trials; and strategies for overcoming drug resistance. International sessions at the 9th Annual Meeting of the JSMO, held in Yokohama, Japan from July 21 to 23, 2011 addressed these issues. The meeting also held a joint symposium with the American Society of Clinical Oncology. Due to space constraints this report will highlight only topics related to thoracic cancer, including controversies in the treatment of advanced cancer, thoracic-related cancer, such as lung cancer and esophageal carcinoma, and biomarkers.

Controversies in the treatment for advanced cancer

The international session of the Annual Meeting of the Japanese Society of Medical Oncology (JSMO) began with American Society of Clinical Oncology (ASCO)/(JSMO) Joint Symposium. This session addressed controversies in the treatment for advanced cancer and was delivered by Isamo Okamoto (Kinki University, Japan), Suresh Ramalingam (Emory University, Atlanta, GA, USA), Ghassan Abou-Alfa (Memorial Slon-Kettering Cancer Center, New York, NY, USA), Junji Furuse (Kyorin University, Japan), Takayuki Yoshino (National Cancer Center Hospital East, Japan), and Mark Ratain (the University of Chicago, IL, USA).

Dr Okamoto explored current paradigms in chemotherapy, "switch maintenance" and "continuation maintenance", for the treatment of non-small-cell lung cancer (NSCLC). Switch maintenance describes the paradigm using a third agent initiated before disease progression and after the completion of platinum-based combination chemotherapy. Continuation maintenance, which involves the continuation of agents already part of the initial platinum-based combination therapy, has been a focus of therapy already; this strategy is already employed for bevacizumab, despite no clinical trials having specifically investigated its usefulness.

For NSCLC patients with a wild-type epidermal growth factor receptor (EGFR) status, platinum-based combination chemotherapy is the standard first-line treatment. Dr Ramalingam described that recently the use of maintenance therapy following four cycles of chemotherapy for patients with stable disease has demonstrated improved overall survival. In a phase III study, pemetrexed was superior to a placebo in terms of progression-free survival and overall survival as maintenance therapy. Gefitinib has also demonstrated a benefit as maintenance therapy, though efficacy improvement was noted primarily in patients with an EGFR mutation. Taken together, maintenance therapy has emerged as an option for advanced NSCLC patients that derive benefit from first-line combination chemotherapy. Furthermore, Ramalingam pointed out that switch maintenance is considered the evidence-based approach. Though continuation maintenance is also efficacious, the impact on survival is not yet known. His approach is to use maintenance therapy for patients with symptomatic disease or high cancer burden

(volume) and an observation-alone strategy for all other patients.

Given the widespread incidence of hepatocellular carcinoma (HCC) worldwide and the multidisciplinary approach needed for the management of the disease, controversies in management still exist. Dr Abu-Alfa described that until recently treatment of advanced HCC lacked a standard of care. Sorafenib, a multikinase inhibitor, has shown to improve the survival of patients with advanced HCC in randomized clinical trials by Llovet in 2008 and Cheng in 2009. Although these two studies helped establish a new standard of care for the management of advanced HCC, some issues in treatment are still open to debate. The management of HCC is generally influenced by the degree of cirrhosis accompanying the disease. The use of sorafenib in the more advanced stages of cirrhosis, for example Child-Pugh B and C, remains a subject of concern and debate.

Dr Furuse explained transcatheter arterial chemoembolization (TACE) as standard therapy for patients with advanced HCC who are not suitable candidates for hepatectomy or local ablation therapy. In Japan TACE is generally repeated according to tumor viability, as long as liver function is preserved. However, most patients treated with TACE show early disease progression and it is expected that the efficacy of TACE may be improved with adjuvant chemotherapy. Sorafenib is expected to enhance the efficacy of TACE. A randomized placebo-controlled trial of sorafenib after TACE was conducted in Japan and Korea. The primary endpoint was the time-to-progression (TTP) after TACE. The median TTP was 5.4 months in the sorafenib group and 3.7 months in placebo group, which was not statistically significant. There was a discrepancy in the results of a subgroup analysis between Japan and Korea. The duration of treatment was longer in Korea than in Japan. Dr Furuse said the results may be mainly attributable to the patients' background of viral infection, tumor stage and age.

Dr Yoshino discussed the use of anti-EGFR antibodies for the treatment of metastatic colorectal cancer (CRC) with KRAS p.G13D mutation. Previous studies have reported that 30 to 40% of metastatic CRC patients have KRAS mutations mainly located in the codon 12 and 13 and had no response to EGFR antibodies. Dr Yoshino reported that cetuximab might have therapeutic benefits in p.G13D-mutated metastatic CRC patients and that the clinicopathological features of the p.G13D mutation were different from those of wild-type KRAS and other mutations. This suggests that p.G13D-mutated metastatic CRC might have a different response to treatment from those with other KRAS mutations. A prospective randomized phase III trial is being planned to evaluate the therapeutic effect of cetuximab compared to best supportive care in patients with p.G13D-mutated chemotherapy-refractory metastatic CRC in Europe and Japan.

Dr Ratain discussed incorporating pharmacogenomics studies into phase III cancer clinical trials. Clinical oncologists have commonly collaborated with scientists and pathologists on studies of tumor specimens obtained from patients enrolled in phase III clinical trials. Such studies have usually used formalin-fixed paraffin-embedded specimens, although some investigators have also collected fresh frozen specimens for future use. The analysis of such tissue specimens has provided great insights into the variability of human cancer and has in some cases identified tumor biomarkers predictive of drug response. More recently, some investigators have routinely collected germline DNA (isolated from peripheral blood) from patients in phase III trials for the purpose of correlating heritable variants with drug response (both toxicity and efficacy). This has now become routine in cancer and leukemia group B and has led to a major collaboration between NIH Pharmacogenomics Research Network and the Riken Center for Genomic Medicine for genome-wide associations studies.

Lung cancer

Progress in the management of advanced NSCLC, including molecular-targeted therapy, were discussed by Akira Inoue (Tohoku University Hospital, Japan), Manabu Soda (Jichi Medical University, Japan), Seiji Yano (Kanazawa University Cancer Research Institute, Japan), Tony Mok (The Chinese University of Hong Kong, Hong Kong), and Keunchil Park (Sungkyunkwan University, Korea).

Dr Inoue presented the recent advances of mutation-based clinical trials of EGFR tyrosine kinase inhibitor (TKI) in Japan. Initially, EGFR-TKI was used in an unselected population of advanced NSCLC, which mostly had disappointing results in clinical trials. However, the great discovery of sensitizing the mutation of EGFR caused a big paradigm shift in the treatment strategy of EGFR-TKI. Several phase II studies of individualized treatment with gefitinib for patients with EGFR-mutated NSCLC have been reported from Japan, where incidence of such mutations is much higher than that in western countries. The data from these small trials were finally combined as I-CAMP, showing a high response rate (76%) and long median progression-free survival (PFS) of 9.7 months in 148 EGFR-mutated NSCLC patients. Recently, two large phase III studies conducted in Japan (NEJ002 and WJTOG3405) demonstrated a significant superiority of gefitinib against the standard chemotherapy on PFS as the first-line treatment for EGFR-mutated NSCLC patients. Based on this evidence, EGFR-TKI became the standard first-line treatment for EGFR-mutated NSCLC worldwide.

Using his original cDNA expression library system, Dr Soda discovered a novel fusion gene between EML4 and ALK that can be identified in 4 to 5% of NSCLC patients. He explained that fusion of EML4 induces a constitutive dimer-

ization of the ALK kinase domain, and thereby marks its activation. To address whether this fusion protein plays an essential role in the carcinogenesis of NSCLC, Dr Soda established transgenic mouse lines that express EML4-ALK specifically in lung alveolar epithelial cells. Surprisingly, all these mice developed hundreds of adenocarcinoma nodules in both lungs within a few weeks after birth but oral administration of an ALK inhibitor successfully cleared the nodules from the mice. This finding provides candidates for a therapeutic target as well as for diagnostic molecular markers for this intractable disorder.

Dr Yano explained that EGFR T790M second mutation, MET amplification, and high expression of hepatocyte growth factor (HGF), have been identified as clinically relevant mechanisms of acquired resistance of EGFR-TKI in EGFR-mutated lung cancer. Dr Yano presented his cohort study with Japanese lung cancer patients with an EGFR mutation. He found that the high expression of HGF was the most frequent mechanism of three factors of, not only acquired but also intrinsic, resistance to EGFR-TKI. This indicates the rationale of targeting HGF-MET for more successful treatment of EGFR mutant lung cancer with EGFR-TKI.

Meanwhile, Dr Mok described randomized comparative studies that established the use of EGFR-TKI as the first-line therapy for patients with EGFR mutation at exons 19 and 21. The first one was the Iressa Pan-Asia Study (IPASS), which demonstrated a superior response rate and progression-free survival (hazard ratio 0.48, 95% confidence interval 0.36–0.64, $P < 0.0001$). Other studies from Korea, Japan, and China have also shown the same result. Patients with EGFR mutation should be treated with EGFR-TKI irrespective of age, gender, and ethnicity, while patients without the mutation should be treated with systemic chemotherapy. To optimize the treatment outcome of targeted therapy, a physician must be able to identify patients with the mutations, select the best TKI, combine EGFR-TKI with chemotherapy or anti-angiogenic drugs, understand the mechanism of resistance, and investigate novel targets.

There are several important lessons to learn from EGFR-TKI. Dr Park argued that there is an ethnic difference in tumor biology as well as toxicity profile. Accordingly, the clinical outcome of EGFR-TKI and potentially other targeted agents caries and should be taken into consideration in the future design of clinical trials. More recently, activating mutations or translocation of the anaplastic lymphoma kinase (ALK) gene have been identified in several types of cancer including NSCLC. In an open label phase I trial of crizotinib, an oral ATP-competitive selective inhibitor of ALK and MRT tyrosine kinase, the overall response rate was 57% with 6-month PFS of 72% in 82 patients with advance ALK-positive disease. This has defined another segment of NSCLC patients. With the advent of precise molecular medicine, more patient segments, including HER2, BRAF, PIK3CA, AKT1, MAP2K1 and MET, are being identified. This precise molecular segmentation of NSCLC will lead to more accurate positioning of targeted agents which will definitely improve survival of this devastating disease.

Biomarkers

What is the current progress of biomarkers application for cancer subtyping, and for recurrence and prognosis prediction? These questions were discussed by Yi-Long Wu (Guangdong Lung Cancer Institute, China), Rolf Stahel (University Hospital, Zurich, Switzerland), Wataru Ichikawa (National Defense Medical College, Japan), and Yung-Jue Bang (Seoul National University, Korea).

Dr Wu delivered the topic of molecular events in the NSCLC of Chinese patients. Significant molecular advances, such as DNA and RNA sequencing, SNP genotyping, mRNA and microRNA quantification, molecular pathway analysis and integrative bioinformatics, have greatly expanded knowledge of the molecular basis of tumor progression and individual treatment response. There are big differences in the molecular events of lung adenocarcinoma between the East Asian population and Western population. The EGFR mutation is higher in the Chinese population than in the Western population, but KRAS mutation is higher in the Caucasian population. The EML4-ALK fusion mutation may be also higher in the Chinese population than in the Western population. Based on this, the target treatment strategy for NSCLC needs to be carefully considered. In the future, combinations of biomarkers will lead to much more accurate individual treatment for lung cancer. However many of the biomarkers require interventional validation by the scientific community.

The rarity of patients harboring tumors with distinct molecular characteristic means a large network of sites to detect eligible patients is required. To address this challenge, Dr Stahel explained that the European Thoracic Oncology Platform (ETOP) was established in 2009 to promote collaborative research into lung cancer. This Lungscape project coordinates and harmonizes the procedure among lung cancer specialists working in translational research across Europe and facilitating high-quality analysis of larger series of cases.

Dr Ichikawa presented the current potential molecular markers, such as dihydropyrimidine dehydrogenase, orotate phosphoribosyl transferase, thymidine phosphorylase, and thymidylate synthase, for gastrointestinal cancers. Unfortunately, none of these have been implemented in the standard of care for gastrointestinal cancer patients. The majority of the published studies concern a retrospective analysis of data from relatively small-sized and underpowered studies. More definite results can only be expected when these markers are included in the prospective randomized studies.

Traditionally, oncologists try to individualize treatment based on clinical and pathological parameters, such as performance status of the patient, disease-free interval and histological subtype of the tumor. Dr Bang said that now it is possible to identify patients who are either likely or unlikely to respond to a particular targeted agent base on biomarkers. For example, we use EGFR-TKI for patients with NSCLC with EGFR mutation. We also combine trastuzumab with chemotherapy for patients with HER2 positive breast cancer or gastric cancer.

Esophageal carcinoma

Perspectives and latest findings in the field of esophageal carcinoma were delivered by Sung-Bae Kim (University of Ulsan, Seoul, Korea), Hiroki Hara (Saitama Cancer Center, Japan), Yasunori Akutsu (Chiba University, Japan), Satoshi Itasaka (Kyoto University, Japan), and Laurent Bedenne (Federation Francophone de Cancerologie Digestive, France).

Challenges in esophageal cancer were explained by Dr Kim. Although there has been significant improvement in survival over the past three decades, esophageal cancer remains a highly lethal disease. Company-initiated clinical trials on esophageal cancer are rare in Asia compared to those of both prevalent Western cancers, such as lung cancer, breast, and colon cancer, and prevalent Asian cancers, such as gastric and hepatocellular carcinoma. Surgery has always been considered the most effective way of ensuring both locoregional control and long-term survival for resectable esophageal cancer patients. However, surgery alone or any single modality fails in most patients, which has led to many oncologists embracing a multimodality approach.

Dr Hara presented a feasibility study on neoadjuvant chemotherapy with docetaxel, cisplatin and fluorouracil (DCF) for clinical stage II/III esophageal squamous cell carcinoma (ESCC). He found in his study that according to the RECIST criteria, overall response rate was 64.3% after completion of DCF. In the study conclusion, he stated that neoadjuvant DCF was well tolerated and antitumor activity was highly promising. His team is preparing a three-arm phase III trial comparing cisplatin-fluorouracil, DCF and chemotherapy as a neoadjuvant therapy for locally advanced ESCC.

Neoadjuvant chemoradiotherapy (neo-CRT) for advanced ESCC was discussed by Dr Akutsu. Previously, his team revealed that patients with T4 tumor, patients who have five or more metastatic lymph nodes (LN), and patients who have metastatic LN in three fields (neck, mediastinal and abdominal region) have a poor surgical outcome, even when curative surgery can be performed. He therefore performed neo-CRT on such far-advanced esophageal carcinoma. In his study, he concluded that neo-CRT is useful mainly because it can reduce the number of metastatic LN, which is the strongest indicator for the survival in ESCC.

Dr Itasaka discussed the progress of intensity modulated radiation therapy (IMRT) for esophageal cancer. Target dose concentration and reduction of normal organ dose are the key challenges for radiation therapy. IMRT is a promising method for achieving this goal. His study found that an IMRT plan can achieve better dose distribution and can reduce dose for normal organs compared to 3D-CRT. However, because of multiple fields, a widespread low dose area was observed. Lung dose should be carefully evaluated especially for thoracic esophageal cancer.

Dr Bedenne analyzed early salvage surgery after failure of chemoradiation in locally advanced thoracic esophageal cancer. The FFCD 9102 trial shows a similar survival rate for chemoradiation alone and chemoradiation followed by surgery for patients that respond to initial chemoradiation. In the present study, the outcome of non-randomized patients was considered in order to determine if salvage surgery after real or apparent failure of chemoradiation was beneficial. The study suggests that for patients with locally advanced thoracic esophageal cancers, especially epidermoid, salvage surgery after real or apparent failure of chemoradiation can be beneficial and should be considered for patients who are still operable. For doctors and patients wishing to avoid systematic surgery, the convenient strategy might be to deliver chemoradiation with no more than 50 Gy, and consider salvage surgery in the case of proven persistent or recurrent tumor in the mediastinum, without distant metastases. In order to validate this strategy, a randomized trial should be set up to compare it with neoadjuvant chemoradiation systematically followed by surgery.

Summary

This conference not only delivered important new insights, but also raised some questions. What will be the next controversies in treatment against advanced cancer? What will be the next clue from EGFR in lung cancer? Can all cancer, one day, be accurately subtyped by its biomarkers? And, what is the best approach to combine multiple modalities in the treatment of esophageal carcinoma?

More definite answer may only be expected when these issues are translated into the design of prospective studies. This would be a starting point for better cancer treatment in the future.