Editorial

Perspectives in drug development for cancer therapy in Asia

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It is my great pleasure and honor to participate in the editorial committee of the Journal of *Chinese Clinical Oncology*, and I would like to celebrate the successful launching of the official journal. The recent rise of the Chinese Society of Clinical Oncology with the accountability for cancer care and strong leadership in the field has been welcomed by many societies of oncology around the world such as JSMO, KACO, ASCO, and ESMO for the further collaborative efforts to eliminate the burden of cancer patients. In the last September, the 15th annual meeting of CSCO was successfully held in Beijing, and more than 30,000 internationally recognized oncologists around the globe attended to give informative and educational lectures to the participants. The success of the meeting is clearly indicative of the anticipation from many countries for the partnership with the organization to form coalition in a war on cancer, and it is believed that its contribution to development of cancer treatment is more inevitable than ever.

Asia as an epicenter of drug development

For decades, a vast majority of evidences applied for the patients care have been created in western countries, and extrapolated for those with Asian ethnicity. Recently, the emerging Asian countries such as China, South Korea and Japan conduct large phase III trials and provide evidence for a certain population in which a molecular targeted therapy is quite efficacious. Among them are trials comparing the epidermal growth factor receptor kinase inhibitors (EGFR-TKI), gefitinib or erlotinib to the conventional chemotherapies in the patients with non-small cell lung cancer with EGFR mutations (1-3). There had been anecdotal evidence that gefitinib was efficacious in female, non-smoker, Asian patients with lung adenocarcinoma since 1998 when clinical trials for the drug were initiated in Japan, UK and United States. Thereafter, IPASS study was launched to test the hypothesis in Asian population, and the first to provide the evidence that the drug is preferentially of benefit to EGFR mutants through its pre-planned subset analysis by EGFR gene status (4). The study enrolled non-selected population in terms of EGFR gene status, and successfully demonstrated that gefitinib benefits only patients whose tumors harboring EGFR mutations, but not counterparts. Not long after, three phase III trials comparing conventional chemotherapies with EGFR-TKIs in the selected population for EGFR mutations were reported from Japan and China with consistent results of advantage of EGFR-TKIs (1-3). The advent of the molecular targeted medicine is linked to the dramatic improvement of the clinical outcome in patients with NSCLC with EGFR mutations (5).

Furthermore, recent advances in understanding of molecular biology of lung cancer, which was led by Japanese researchers based on the findings using clinical specimens, allows us to take further steps toward more personalized and sophisticated strategies for those people who live with lung cancer. Soda and colleagues infected mouse 3T3 fibroblasts with a retroviral cDNA expression library prepared from a lung adenocarcinoma resected from a 62-year-old male Japanese patient, and the EML4-ALK fusion gene was identified as a potentially targetable oncogenic driver in non–small cell lung cancer in 2007 (6). An ALK inhibitor, crizotinib was approved in Japan for the patients with NSCLC with EML4-ALK fusion gene in 2012, following the promising results of the expanded cohort phase I trial conducted in multiple countries including South Korea (7). It is noteworthy that these two drugs were approved in

extraordinarily swift processes, within 4 years from the initiation of clinical trials, and could not have been that successful without the coalition from Asian countries. In other words, the approval of the molecular targeted medicine in lung cancer would have been delayed for many years without collaboration of China, South Korea and Japan. Furthermore, many clinical trials for molecularly-selected patients (e.g., LUX-LUNG3 and IMPACT trial) are ongoing in Asia, and even more paradigm shifts of the therapies for lung cancer patients are on the way. Taken together, it is safe to say that leadership and participation of Asian countries in drug development process has become a key element to the success in establishment of molecular targeted therapies for cancer, and no doubt that Asia is already an epicenter of drug development for lung cancer.

Government funded-training program of oncologist

Asia's prevalence of cancer deaths may climb 45 percent to 163 per 100,000 people by 2030, from about 112 per 100,000 in 2005, according to the World Health Organization and establishment of organized and coordinated medical care is warranted to reduce the burden of cancer in the region. To this end, what is needed most here are human resources which abundantly supply specialists who are well trained and experienced in cancer cares. Each country must make further efforts to establish the comprehensive training program for oncology specialist, and assure that the multidisciplinary approach is always available to address the complicated issues surrounding cancer patients. Cancer Control Act was enacted 2006 in Japan and subsequently Training Program of Oncology Specialist for medical staff has been initiated since 2007 as the government-funded program in order to reduce disparities existing among the regions in the country in terms of quality of cancer care. Academia plays a major role in implementing the program, and quality of care for the cancer patients has been gradually improved in the areas. Given the importance of international collaborative efforts for drug development in Asia, the program has been amended recently to expand its scope and incorporate an initiative for training of cancer researchers who collaborate with international partners. This amendment, aimed to improve the quality of international collaboration, would globalize their cancer researches and care, and accelerate innovation of diagnostic tools and cancer therapies from the Asian region. Formation of an international collaborative group for cancer research in Asia may be a plausible milestone if our effort has paid off.

Academic research organizations and collaborative clinical trial groups

The enrichment of the population by biomarkers for expensive medicines would alleviate financial distress of each country in the long run and also improve safety profile of treatments. It is important to pursue translational research in each clinical trial in order to find biomarkers that identify a subset of patients with maximized therapeutic index. Non-selected application of such pricy medicines without any evidences of improved quality of life or survival is no longer a realistic option, and regulatory approval of molecular targeted medicines may require labeling with enriched population use in future. Thus, collaborative work of clinical department and laboratory has been an essential component of drug development, and it is almost mandatory for academic institutions and cancer centers which initiate drug development to establish the network involving multiple clinical departments and laboratories, and form academic research organizations (ARO).

The current environment of clinical trials is harsh with the high costs, more burdensome regulatory requirements and the slim chance that a new compound will actually make it from the laboratory to the pharmacist's shelves (8). Diseases are being classified in narrower and narrower ways, and more rigorously defined disease categories enhance the development of targeted therapies, but could also impede trial enrolments: the more specific the therapeutic target gets, the longer it can take to enroll the numbers required to conduct a statistically rigorous study. As mentioned before, the incorporation of biomarkers into clinical trials could also slow down enrollment. The environment makes pharmaceutical companies increasingly reluctant to invest for a new chemical developed into a regulatory-approved medicine despite the pressure of looming patent expirations of the older drugs in their inventory. These contexts put collaborative clinical trial groups (CCTG) into interesting position; pharmaceutical industries now show some interest in taking a collaborative approach to conduct clinical trials through CCTGs, albeit the issue about slow enrollment and sky-rocketing cost for drug development will force CCTGs into a merger and a task force in future.

Today, the roles Asian countries play in the field of drug development are significant and cannot be neglected. As I have mentioned in the passages above, there are multiple ways by which Asian countries can contribute

to the development of cancer treatment, such as genetic characteristics, quality educational systems and clinical trial environment. I sincerely hope that Journal of *Chinese Clinical Oncology* may continue to enrich the knowledge base of the oncologists in Asia and serve the advancement of cancer treatment of the world.

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