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EDITORIAL

Mission of the National Cancer Center Hospital in Japan to promote clinical trials for precision medicine

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Precision medicine is a growing field worldwide. Despite its potential benefit to many patients, several major obstacles must be overcome before precision medicine can be more widely used in clinical practice. The main obstacles are associated with the quality of samples used for genomic analysis, difficulty in interpreting analysis results, difficulty of patient enrolment due to fragmentation of trial participants by defining eligibility criteria with rare biomarker, coverage and reimbursement by national health insurance schemes, and the cost of genomic analyses and targeted drugs. In this special issue of Cancer Biology & Medicine, we feature precision medicine and clinical trials, with a focus on Japan and other Asian countries. Japan has established several national initiatives associated with cancer genomic medicine and a nation-wide system to bring genomic medicine to community hospitals across the country. We hope that sharing these experiences will help researchers and policy makers in other countries introduce cancer genomic medicine to their own populations.

Under the vision of providing the best possible cancer treatment and care through a committed partnership with the community, the National Cancer Center Hospital (NCCH) Japan has functioned as a hub hospital for cancer therapy in Japan; provided optimal medical treatment for individual patients with cancer; and undertaken high-quality clinical research to discover more effective, safer, novel medicine since its establishment in 1962.

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As a national flagship cancer center, NCCH has been a leader in cancer genomic medicine from its establishment. In addition to exploring leading edge technology, our activities have included planning the best way to introduce state-of-the-art cancer genomic medicine into clinical practice in community hospitals. Since the 2000s, next-generation sequencing-based molecular screening has shown promise and potential for selecting the most appropriate patients for entry into clinical studies[1]. In a first step, we evaluated the feasibility and utility of the NCC Oncopanel test in TOP-GEAR projects (UMIN000011141), which were developed by the Research Institute of the National Cancer Center[1]. After confirming its clinical utility at the single-institution level, we next conducted a nation-wide clinical study under the Advanced Medical Care B program in early 2018 to assess the feasibility of implementing the NCC Oncopanel on a multi-institutional basis (UMIN000032166). A total of 343 patients were enrolled within 8 months. After the success of the trial, the OncoGuide® NCC Oncopanel system was simultaneously approved as a medical device along with the Foundation One® CDx system in December 2018[2-4]. Furthermore, since June 2019, cancer genomic profiling tests—when performed at government-designated hospitals with a molecular tumor board composed of multidisciplinary specialists, referred to as an expert panel (EP)—have been reimbursed by the National Health Insurance system in Japan.

Standardization of EPs is a critical challenge in implementing precision oncology in clinical settings. The EP discusses genetic alterations found in the Comprehensive Genomic Profiling (CGP) test and recommends the most appropriate medicines according to the Clinical Practice Guidance for Next Generation Sequencing in Cancer Diagnosis and Treatment[5]. Medical oncologists explain the content of final reports produced by the EP to patients, who can then choose

to receive the recommended therapy, if available, after providing informed consent. However, on the basis of our research, only 10%–20% of patients have genetic alterations that make them candidates to receive targeted therapy, although more than 50% of patients who receive a CGP test have actionable gene alterations[6]. According to a national survey, this percentage was as low as 8.1% in the first year after the National Health Insurance system began covering CGP tests[7]. The primary reason for this low treatment rate is the insufficient number of gene-matched drugs approved or in clinical trials. Although NCCH had conducted 507 registration-directed trials (447 industry-sponsored and 60 investigator-initiated trials) and 230 non-registrational investigator-initiated trials as of April 2022, the proportion of patients receiving matched drugs remains insufficient.

To resolve this problem, NCCH promoted a platform trial called the BELIEVE (NCCH1901) trial, in October 2019, to increase the chance of patients who had undergone CGP testing receiving off-label drugs (jRCTs031190104). This trial was conducted under the Patient-Proposed Health Service, which enables partial reimbursement for administered off-label drugs under the National Health Insurance system. As of September 2022, 20 off-label drugs from 7 industries were available under the BELIEVE trial.

Another initiative aimed at promoting precision medicine is the MASTER KEY project (UMIN000027552), which combines an academia-industry collaborative registry study of patients with rare cancers with multiple investigator-initiated or industry-sponsored registration-directed trials[8]. Our main reason for focusing on rare and refractory cancers is the large number of unmet medical needs associated with these diseases. The initiative, which was launched in 2017, is developing a comprehensive clinical and genomic database of rare cancers and aims to use registry data as historical control data to facilitate efficient investigator and industry-initiated registration-directed trials. As of January 2022, more than 2,000 patients with solid cancers and more than 200 patients with hematological cancers were enrolled in the project—more than initially expected. Registered patients have gained access to 10 industry-sponsored trials and 10 investigator-initiated trials including patients with rare cancers. A unique aspect of the MASTER KEY project is that it includes many investigator-initiated registration-directed trials developed in accordance with the Japanese regulatory framework, thus enabling academic investigators to serve as regulatory sponsors and develop clinical trial data for pharmaceutical application. In fact, NCCH received approval for the world's first drug for unresectable thymic carcinoma through an investigator-initiated registration-directed trial[9].

International collaboration plays an important role in promoting precision medicine. In September 2020, we launched the Asian clinical TriaLs network for cAncerS (ATLAS) project with a grant from the Japan Agency for Medical Research and Development, a public funding agency in Japan. Through this project, and by building on new clinical trial network with researchers or investigators in developped nations and regions in Asia, we will support the building of infrastructure needed for clinical trials in fast-growing ASEAN countries, establish an early phase drug development network in Asia, provide equipment and training programs, employ specialists, and conduct multiple international collaborative clinical trials to promote precision medicine. The number of industry-sponsored trials being conducted in this region is low, particularly for rare cancers, thereby limiting treatment options. We expect that promoting investigator-initiated trials will encourage collaboration and in turn help Asia address unmet needs in the region. Furthermore, we anticipate that the ability to recruit more patients in a wider region will accelerate the development and delivery of new drugs. This clinical trial network in Asia should facilitate drug development worldwide. For example, we are expanding our MASTER KEY project to Asian countries, accelerating patient accrual in the rare cancer registry, and facilitating more clinical trials for patients with rare cancers in Asia.

Greater proactive action is also needed to develop new clinical trial strategies in this precision medicine era, because traditional randomized controlled trials, the gold standard for clinical trials, are often have high financial and time costs. In addition, stringent inclusion criteria may decrease external validity. Given the time sensitivity of many drug trials, particularly in the case of orphan drugs, evidence from real-world applications is expected to play a major role in many areas of evidence-based medicine in the future[10,11]. In fact, because most investigator-initiated registration-directed trials in the MASTER KEY project are single-arm trials, registry data will serve as robust historical data and will be used as real-world evidence of comparison with clinical trial data. Other important attempts to innovate in clinical trials include making practical use of master protocols consisting of umbrella trials, basket trials, or platform trials to identify target tumor subtypes or mutations, as well as introducing decentralized clinical trials that use various types of electronic data to promote drug development, improve expedited drug approvals, and decrease costs[12].

In summary, genome screening tests, which will undoubtedly be useful for selecting appropriate patients for entry into clinical trials, have been widely used after their coverage and reimbursement was approved by the universal health insurance scheme in Japan. Acceleration of novel and optimized clinical trials based on molecular profiling will be critical in increasing the number of gene-matched drugs available to patients.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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