International models of investigator-initiated trials: implications for Japan


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Background: Academic/institutional investigator-initiated clinical trials benefit individuals and society by supplementing gaps in industry-sponsored clinical trials.

Materials: In May 2010, experts from Japan, the Republic of Korea, the UK, and the United States, met at a symposium in Tokyo, Japan, to discuss how policies related to the conduct of clinical trials, which have been shown to be effective, may be applied to other regions of the world.

Results: In order to increase the availability of anticancer drugs world-wide, nations including Japan should examine the benefits of increasing the number of investigator-initiated clinical trials. These trials represent one of the most effective ways to translate basic scientific knowledge into clinical practice. These trials should be conducted under GCP guidelines and include Investigational New Drug application submissions with the ultimate goal of future drug approval.

Conclusions: To maximize the effectiveness of these trials, a policy to educate health care professionals, cancer patients and their families, and the public in general on the benefits of clinical trials should be strengthened. Finally, policies that expedite the clinical development of novel cancer drugs which have already been shown to be effective in other countries are needed in many nations including Japan to accelerate drug approval.

Key words: academic/institutional investigator-initiated clinical trials, anticancer drugs, good clinical practice, health care policy, international clinical trials, patient advocates

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Introduction

In May 2010, representatives from the Health and Global Policy Institute (Tokyo, Japan), together with experts from the UK, the Republic of Korea (ROK), Japan, and the United

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States met in Tokyo, Japan, to discuss their strategic plan and future directions of clinical trials (information on the speakers and the program of Japan–ROK–UK–United States Workshop is provided as supplementary data, available at Annals of Oncology online). The current paper examines how best practices in cancer clinical trial programs of the four participating countries could be further adopted by each other, from the viewpoint of local, national, and international concerns.

**national issues**

**accessibility of investigational agent by academia/institution investigators**

As evident by the success in the United States and the UK, the importance of investigator-initiated trials in drug development and in defining cancer care best practices should be recognized for its key role by government officials. As the best available indicator, the number of investigational agents accessible for investigator-initiated trials is deemed crucial for the conduct of clinical trials in the public health care system. The source of these agents can be identified and provided by the three different stakeholders, pharmaceutical or biotech companies, academia or private institutions, and the government. Accessibility to pharmaceutical or biotech company-derived investigational agents is most important to promote investigator-initiated clinical trials. In the United States, availability of these agents among academia or private institutional investigators is facilitated by the federal government.

An excellent example of a recent national comprehensive strategy is the Korean National Technology Roadmap Project in 2002. In the context of Korea National Technology Roadmap, clinical trial was recognized as an important future health care technology with knowledge-based economy by government level. This project’s Experts Working Group on Clinical Trials recommended globalization of clinical trials, establishment of centers of excellence, development of educational and training programs for clinical trials professionals, international accreditation of ethics committees, early regulatory reforms of old new drug approval system, and investigational exemption of new drug trials equivalent to ICH guidance.

Another example of a success model is seen in the ongoing British partnership between the UK National Cancer Research Network (NCRN), AstraZeneca Pharmaceuticals, and Cancer Research UK for the support of phase I/II trials. The NCRN can run three different models of trials, including academic trials without industry support, academic trials with some additional support from industry, and commercial trials, which are reviewed by the NCRN for scientific merit and ‘fit’, i.e. feasibility of accrual within the national trials portfolio.

In the United States, the federal government supports the development of novel compounds by facilitating first in human clinical trials (NExT program, [http://next.cancer.gov](http://next.cancer.gov)). Novel agents developed in the federal government institutions are also available to the academia/private institution investigators for further clinical development. The US NCI holds more than 80 active clinical trials agreements with pharmaceutical companies to conduct phase I, II, and III clinical trials by academic/institutional investigators. In particular, NCI Cancer Therapy Evaluation Program (CTEP) has been actively utilizing cooperative research and development agreement (CRADA) between industry and the federal government to promote and support extramural academic/institutional investigators’ accessibility to new investigational agents.

In contrast, a number of novel investigational agents which are under early clinical phase studies outside of Japan are not available to Japanese academia/institutional investigators. Therefore, the majority of investigator-initiated trials in Japan use on-label drugs which do not have any issues for drug accessibility. The reason for conducting on-label drug investigator-initiated trial stems from the Japanese public health insurance system, which does not permit off-label drug use in clinical trials except for a specified case such as trials conducted under ‘Evaluation System of Investigational Medical Care’, also mentioned in what follows. However, if the investigator proposes an investigator-initiated trial using Investigational New Drug (IND) application toward drug approval and the pharmaceutical company agrees to do this type of trial, then the investigator can access new drugs provided by the company. The Japanese government generally requires phase 1 data from Japanese subjects in order to introduce a new investigational agent into the country, and this requirement cannot be fulfilled by phase 1 data from other races, which becomes a potential limiting step in the process of novel drug development in Japan. Other potential sources of delay may include insufficient infrastructure, regulatory-related issues, and the level of support by the government for early-phase drug studies. Government’s proactive collaboration with industry and academia/institutions to bring in novel agents would facilitate investigator-initiated clinical trials by Japanese investigators.

**expanding anticancer agent indication to other tumors after new drug application**

In the ROK, the use of non-approved or off-label drugs is not reimbursed by the National Health Insurance (NHI) unless cases are reviewed and approved by special committee upon request from qualified hospitals based on evidence.

In Japan, the cost of cancer therapy is reimbursed by the NHI and is based on the approval of the drug for specific cancer types. Adding additional cancer types to an approved drug’s indication usually entails additional clinical trials and delays drug availability for these new indications. In the United States, to minimize the time gap between initial agent approval for other tumor indications, the NCI CTEP works closely with industry at a very early stage of agent development. These collaborations facilitate the timely initiation of NCI-sponsored clinical studies in tumors that industry was not seeking an indication. With this effort, the very first antiangiogenic agent bevacizumab has achieved clinical indications for several different tumor types and stages within a relatively short period of time after the company’s registration trial gained new drug application. Such proactive efforts may not be possible in all countries. As an alternative, acceptance of scientifically sound data from other countries to be used for the approval of a new
drug indication should be considered. Likewise, the Japanese authority allows evidence in literature to substitute results of clinical trials in approving ‘old’ anticancer agents for specific types of cancer. The agents which are not chosen for this approval process must be tested by clinical trials in the Japanese population.

The present requirement by Japanese authorities to prove a drug’s safety and efficacy in the Japanese population, even when the drug has been approved abroad, sometimes entails carrying out additional clinical trials in Japan, which delays the introduction of new pharmaceuticals. Although ICH-GCP includes indications for bridging studies, Japan requires it for most drugs developed outside of Japan, except most notably for orphan drugs (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf) [1].

A national strategy to promote investigator-initiated cancer clinical trials

A national commitment to investigator-initiated cancer clinical trials should include a strategy for scientific prioritization of trials, similar to that seen in the ROK, UK and United States (http://transformingtrials.cancer.gov/initiatives/ctwg/prioritization).

Clinical trials should be carried out as a part of public health care, so that patients are screened easily and given the opportunity to participate in trials. A noteworthy example is in the UK, where the NCRN is integrated with the National Health Service. This system increases patient clinical trial enrollment and also ensures that routine patient costs associated with the trial are covered by the NHI system, while the expense of investigational agents is funded by pharmaceutical companies. In Japan, the NHI system covers medical care costs such as consultation, examination, and medication for all citizens. Under this system, reimbursement is limited by NHI to medications administered as indicated in the product labeling. The use of an off-label drug is only permitted, with associated routine care costs covered by NHI, if the clinical trial is carried out for marketing authorization with IND submission under the Pharmaceutical Affairs Act. Thus, the majority of investigator-initiated studies conducted in Japan rarely use non-approved or off-label drugs. To promote investigator-initiated clinical trials in Japan, ‘The Evaluation System of Investigational Medical Care’ was initiated in April 2008 to allow using off-label drugs in clinical trials which are approved by the MHLW Review Board.

Although the new system appears to be attractive to academia investigators from the cost reimbursement aspect, clinical studies conducted under this program are not required to be done according to Japan’s GCP Ordinance, which is compatible with ICH-GCP guidelines. Investigator-initiated clinical trials with IND submission would be more advantageous as it requires compliance with the Ordinance, and the data generated from the trial can be used for future drug approval. However, the complicated process for IND submission is a further barrier to the academic investigator wanting to use off-label or novel agents. The Korea Food and Drug Administration (FDA) does not permit investigator-initiated clinical trials with IND submission. This process is completely different from the US system in which academic/institutional investigators have government-supported infrastructure providing the capability for developing novel investigational agents. In the United States, it is the mandatory process to submit for research INDs for the conduct of early clinical phase studies to the FDA [2]. Novel agents or biologics, for example, anticancer vaccines generated by Japanese academia, are not required to submit an IND application to the regulatory agency or MHLW as long as the agent is tested within the academia/institution of the investigator, and the clinical trial is approved by the institutional review board, regardless of GLP, GMP, or GCP compliance. The Japanese government has realized these clinical trials are problematic, and under the new 5-Year Clinical Trial Activation Plan, 15 core clinical research centers will be established after 2012 at which clinical trials under a GCP Ordinance will be initiated (http://pj.jiho.jp/servlet/pjh/article/detail/1300862106724.html).

To improve participation, the public, including patients and their families, should be educated as to the general value of clinical trials. In addition, practice and theory of clinical trial development should be taught as a part of core curriculum at schools of medicine, nursing, and pharmacy. Those professionals who are involved in conducting clinical trials, namely physicians, research nurses, and pharmacists, need to be trained to fulfill their applicable functions properly. These types of efforts are being made in all of the countries represented in the symposium.

Government’s financial support is also essential in promoting academic/institutional-sponsored cancer clinical trials. The NCRN in the UK provides government funding to develop protocols, in addition to conducting and monitoring clinical trials. In the United States, the NCI underwrites a large portion of the costs for 10 Clinical Trials Cooperative Groups and Phase 1 and 2 consortia, which comprise a network of clinical centers responsible for conducting trials of experimental agents. Likewise, the Korean National Cancer Center has initiated biostatistical and data management support to clinical trial groups. In Japan, as part of the New 5-Year Clinical Trials Activation Plan, core clinical research centers plan and manage multicenter, industry-sponsored clinical trials in a variety of diseases. However, there are only a few centers capable of conducting oncology clinical trials.

Local institutional issues

Institutions and academic centers should have efficient oncology clinical trial centers which can provide scientific, logistical, and ethical review promptly, get new trials opened quickly, and monitor the conduct of trials effectively under ICH-GCP guidelines. An excellent example is the development of 15 clinical trial centers at university hospitals nationwide in the ROK. As per the recommendation of Experts Committee of 2002 National Technology Roadmap Projects, Korea Ministry of Health and Welfare started to fund Regional Clinical Trials Center establishment programs to create the state-of-the-art environment for high-quality clinical trials from 2004 to 2010. The US NCI funds core resources, including clinical trial offices, at the 45 NCI-designated Clinical and Comprehensive Cancer
In addition, the NCI also provides additional support to 15–20 Cancer Centers for phase I and II clinical trials of investigational agents. The UK has also established 19 Experimental Cancer Medicine Centers to conduct both academic and commercial phase I and II clinical trials. These centers are jointly funded by the UK Departments of Health and Cancer Research UK and, in addition to having expertise in early-phase trials, they promote translational research associated with all phases of the trials. As emphasized in Japan’s New 5-Year Plan, local clinical research centers play essential roles in supporting clinical studies scientifically and logistically. In Japan, greater involvement of non-physician health care professionals, such as research nurses, nurse-practitioners, physician’s assistants, and data managers, would certainly allow more time for Japanese physicians to plan and conduct clinical trials.

involvement of cancer patient advocates

Cancer patient advocates play important roles in the education of the public regarding the critical need for clinical trials and medical research. These individuals, who are generally cancer patients or their family members, should also be integrally involved in various clinical trial activities, including trial design, scientific and ethical review, education, promotion, and dissemination of results. However, adequate training must be provided for their optimal integration in these activities [3]. Advocacy groups may also serve as effective ambassadors to national policy makers to explain the importance of clinical trials. Japan Cancer Control Act, implemented in 2007, mandated the inclusion of a patient representative on both the Japan National Cancer Control Promotion Council and Prefectural Cancer Control Councils.

international collaboration

Incentives for international collaboration in conducting cancer clinical trials have become increasingly strong in recent years [4]. The ICH is an excellent example of developing global guidelines for clinical trials. Similar efforts specific to cancer include harmonization of cancer staging, standardization of pathologic classification, efforts to harmonize grading of toxicity and adverse events, and response to treatment. Challenges to international collaboration include differences in national regulations on pharmacovigilance, insurance/indemnity, along with availability of drug supply.

A good example of international collaboration is the joint development of gastric cancer studies between Japan and the ROK, where the incidence of gastric cancer is extremely high [5]. The study was quickly completed to accrual and provided meaningful results. Another exceptional example is the fruitful collaboration among the Breast InterGroup (BIG), the International Breast Cancer Study Group (IBCSG), and the North American Breast Cancer Intergroup in developing guidelines for specimen handling and a research agenda for male breast cancer [6, 7]. In a similar manner, the Gynecologic Cancer InterGroup (GCIG) brings together 21 academic cooperative groups from 15 countries and two regions (Europe and Scandinavia). Also, the UK National Cancer Research Institute, US NCI, and GCIG recently co-sponsored meetings to develop global research agendas for endometrial and cervical cancers [8, 9]. This type of international collaboration can lead to the timely completion of clinical trials and can speed the approval of new drugs in each of the involved countries.

Lastly, the importance of collaboration between regulatory authorities and academia in strengthening the scientific basis for regulation should be emphasized, such as appropriate clinical trial design to meet concomitant research and drug approval objectives. This applies, for example, to establishing international standards in the development/evaluation of cancer drugs. Recently, the three major drug regulatory authorities of the world (i.e. FDA, EMA, and PMDA) published their policies to encourage regulatory science to facilitate drug development and improve their regulatory actions (http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000479.jsp&murl=menus/special_topics/special_topics.jsp&mid=WCO0b01ac05802636c8&jsenabled=true; http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM228444.pdf) [10].

conclusions

The international symposium held in Tokyo, Japan, represented a snapshot of current activities regarding investigator-initiated cancer trials in Japan, the ROK, UK, and United States. Among many factors, formulation of a national strategy, government support, involvement of patient advocates and industry, and international cooperation in various aspects of the trials are of particular importance in promoting investigator-initiated clinical trials. Strengthening of Japanese government support for academia/institutional investigator-initiated clinical trials, and particularly in guiding investigators toward ICH-GCP ordinance together with an improved national clinical trial infrastructure, will facilitate both international collaboration and accelerate new drug availability. Moreover, Japan can benefit from other countries’ successes by employing some of the measures taken abroad to enhance the availability of cancer drugs.

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The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends

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Background: During the past four decades, the incidence of esophageal adenocarcinoma (EAC) has increased markedly in Western populations. Recent reports have suggested that the rate of increase has slowed or plateaued.

Patients and methods: Using data from cancer registries in Australia, the United States and Sweden, we examined incidence trends for esophageal and gastric cardia tumors between 1984 and 2008 using joinpoint analyses and age–period–cohort models.

Results: EAC incidence continues to undergo statistically significant annual increases in Australia and the United States, although the rate of increase has slowed. Among men, incidence increased annually by 2.2% [95% confidence interval (CI) 1.5% to 2.9%] between 1994 and 2008 in Australia and 1.5% (95% CI 0.2% to 2.8%) between 1998 and 2008 in the United States. EAC incidence among men remained unchanged in Sweden between 2001 and 2008 (P = 0.52). EAC incidence among women showed significant linear increases between 1984 and 2008. Age–period–cohort models suggested strong effects for both period and birth cohort on EAC incidence in Australia and the United States, and a strong period effect for Sweden.

Conclusions: EAC incidence continues to increase in Australia and the United States. The continued increases, even among more recent birth cohorts, suggest that EAC incidence will continue to rise during coming decades.

Key words: age–period–cohort models, annual percentage change, epidemiology, esophageal adenocarcinoma, incidence, secular trends

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