W-1 [10:00～10:10]

Recent Progress in Anti-Cancer Agents

Tetsuo Satoh
Biomedical Research Institute, Japan

The development of anticancer agents and the use of the drugs for cancer therapy have been extensively progressed for a past dacade. Populations and individuals are always exposed to cancer risk, and the risk is assessed by the following items.

1. Exposure assessment should be improved by measuring biologically effective doses of carcinogens, such as carcinogen molecular adduct and mutational spectra of cancer-related genes.
2. Analysis of inherited or acquired host susceptibility factors with the framework of epidemiogolocal studies.
3. Cancer susceptibility factors include mutations in tumor suppressor genes, and genes involved in carcinogen mechanism.
4. Inter-individual variation for each of these biologic endpoints as above are needed for assessing cancer risk on an individual basis.

In the cancer therapy, four different approaches, i.e., chemotherapy, immunotherapy, radiotherapy and surgical therapy have been widely used, In this workshop, four Japanese experts in this field(by S.K., H.I., S.N. and Y.S.) will present the update information of the anti-cancer agents from the viewpoints of drug development and advanced therapy. These presentations highlight the importance of strategies of the developments and and clinical therapy update of the novel anti-cancer drugs.

An Overview on Recent Progress of Anti-Cancer Agents(Shinichi Kurakata)
This speaker reviews the recent progress of anti-cancer agents such as cytotoxic agents acting on novel molecular targets. So far so may anti-cencer agents have been developed worldwide against various types of cancers such as against colorectal cancer and lung cancer. The author describes the chronologic background of anti-colorectal cancer. Until the early 1990s, therapeutic options for advanced

colorectal cancer were mainly confirmed to chemotherapy with 5-FU with and without biochemical modulation with leucovorin. At the end of 2001 more than 60 antiangiogenic agents were in clinical trials, including endostatin and angiostatin. While improved survival remains the ul;timate endpoint for oncology trials, the identification, validation and standardization of surrohgate markers fo the antitumor effects of the various cytotoxic agents are turn-key issues for optimizing the development of agents targeting novel molecular targets.

Discovery of Capecitabine(XelodaR) and Its Translation to Clinical Studies
(Hideo Ishitsuka)

The author reviews the development and clinivcal studies of Capecitabine(XelodaR), an anticancer drug. Capecitabine is more potent and has a wider spectrum of antitumor activity than 5-FU, 5'-DFUR and UFT against 24 human cancer xenograft models of colon, breast, gastric,cervical, bladder, ovarian and prostate cancer. In the clinical studies, it was observed that enzyme levels of TP(thymidine phosphorylase), and DPD(dihydropyrimidine dehydrogenase) which are responsible for respectively generating and metabolizying 5-FU, in the tumor tissues affected the susceptibility fo capecitabine. Therapeutic benefits from capecitabine therapy would increase when it is given to patients with high tumor TP/DPD. Capecitabine in combination with additional up-regulators, such as X-ray irradiation, is being clinically assessed with great anticipation.

New Anti-Cancer Agent S-1: Metabolism Based Drug-Combination
(Sekio Nagayama)

S-1 is a novel oral fluorinated antitumor drug that combined three pharmacological agents:tegafur. a prodrug of 5-FU, CDHP inhibiting dihydropyridine dehydrogenase (DPD), and oxonate wich reduces gastrointestinal toxicity. The antitumor activity of S-1 after oral administration is based on 5-FU that appears gradually in the body via the transformation of FT. CDHP increases the concentrations of 5-FU, which is converted from FT, by selectively and reversibly inhibiting DPD,a catabolic enzyme of 5-FU. S-1 is approved in Japan for the treatment of stomach and head and neckcancer. For the colorectal, breast, and lung cancer clinical development are ongoing.

Pharmacokinetic/pharmacodynamic approach for molecular targeting anti-cancer agents

(Yasutsuna Sasaki)

The pharmacokinetics(PK)/pharmacodynamics(PD) analysis of drugs such as anti-cancer agents is well recognized to understand the efficacy and side-effects of the drugs. Because of polymorphism of drug metabolism, there are individual variations in terms of efficacy and toxicity of drugs, and the drug concentrations are monitored to decide the appropriate doses in cancer chemotherapy,

In conclusion, we may see combinatorial chemistry, the computerized design of chemical compounds based on three-dimentional structure, lead to the accelerated development of drugs. Although the human genome project is an important advance, we all recognize that it is proteins, not DNA that are the final messengers that bring cellular function. Proteomics will be a huge engine for change during the next century. We can be confident that DNA vaccines aimed at specific molecular targets will emerge with increasing rapidity as the sciences of genetics and molecular biology surge forward. Genetics and genomics will continue to power scientific advances. They will provide the tools for identifying populations and individuals at high risk for a wide spectrum of diseases, including cancer. Advances in cancer-screening technology focused on these high-risk populations will increase the speed and accuracy of early diagnosis and result in a more efficient and cost-effective system for applying screening interventions. The history of cancer prevention is short. It is the unimagined advances of the next 50 years, The things that we do not now have the tools or vision to forcsee, that will likely make more profound changes than anything that has been discussed here.