PDX clinical trial and co-clinical trial for development of anti-cancer drugs in solid tumors

Yoshikatsu Koga
Department of Strategic Programs
Exploratory Oncology Research & Clinical Trial Center
National Cancer Center

In vitro cell killing assays using commercially available patient-derived cell lines or *in vivo* tumor growth inhibition assays using cell-line derived xenograft (CDX) models, in which these cell lines are transplanted into immunocompromised mice, are commonly employed to measure the efficacy of anti-cancer drugs and to make a decision for further clinical study. Unfortunately, few drugs are approved even if the drugs demonstrate a good response in preclinical studies. Indeed, only 5% of the anti-cancer drugs that have anti-cancer activity in preclinical studies are approved for clinical application by the United States Food and Drug Administration (FDA).

Traditional CDX models consist of many cancer cells but few cancer stromal cells, and they are difficult to use in preclinical models for predicting the response in clinical trials. This prompted attempts to inject patient-derived cancer tissue into immunocompromised mice, which has been conducted for over 40 years. These patient-derived xenograft (PDX) models conserve the biological features of the original tissue. A significant association was observed between drug responses in patients and the corresponding PDX models in 87% (112/129) of therapeutic outcomes; thus, PDX models are recognized as accurate and clinically relevant models[1]. The National Cancer Institute (NCI)-60 panel, which contained 60 human cancer cell lines, was heavily used by researchers around the world for anti-cancer drug screening for over 30 years. In 2016, the United States NCI decided to stop screening of anti-cancer drugs using the NCI-60 panel and focus on newer PDX models[2].

Using large PDX repositories, PDX models have been used for PDX clinical trials in preclinical studies for clinical decision making. PDX clinical trials are important for the development of anti-cancer drugs prior to clinical trials. Co-clinical trials are run in parallel and/or real-time with human clinical trials, and they include mouse trials using PDX models established from the clinical trial participants for assessment of drug response. This approach is recognized as a model for personalized care or precision medicine.

PDX models are used as powerful tools for understanding cancer biology in PDX clinical trials and co-clinical trials. Thus, we focus on PDX clinical trials or co-clinical trials for drug development in solid tumors and summarize the utility of PDX models in the development of anti-cancer drugs[3]. Our research entitled "Survey and research of usefulness and issue on the patient-derived xenograft (PDX) model for the drug development" is supported by the Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Japan Agency for Medical Research and Development (AMED). The aim of this research is to clarify usefulness and issue on the PDX model for the drug development in Japan and the world, and make recommendations of high-quality PDX model to use the PDX model for the drug development.

[Awards]

2014 The Incitement Award of the Japanese Cancer Association
「Development of novel cancer diagnostic methods using exfoliated cancer cells」

[References]

1. Izumchenko E, Paz K, Ciznadija D, et al. Patient-derived xenografts effectively capture responses to oncology therapy in a heterogeneous cohort of patients with solid tumors. ***Ann Oncol***. 2017, 28: 2595-2605.
2. Ledford H. Us cancer institute to overhaul tumour cell lines. ***Nature***. 2016, 530: 391.
3. Koga Y, Ochiai A. Systematic review of patient-derived xenograft models for preclinical studies of anti-cancer drugs in solid tumors. ***Cells***. 2019, 8(5): 418.

Yoshikatsu Koga, MD, PhD
Chief, EPOC, National Cancer Center

1999 Kumamoto University School of Medicine, MD
1999 Kumamoto University Hospital, Resident
2000 Miyazaki Prefectural Nobeoka Hospital, Surgeon
2002 Minamata Medical Center Hospital, Surgeon
2003 Kumamoto University Hospital, Surgeon
2006 National Cancer Center Hospital East, Research Resident
2009 Kumamoto University Graduate School of Medicine, PhD
2011 National Cancer Center, EPOC, Section of Experimental Animals, Head
2019 National Cancer Center, EPOC, Department of Strategic Programs, Chief