Oral

[O27-2] O27-2: Pharmacometrics (2)

Chairs: Fumiyoshi Yamashita, Japan / Toshimi Kimura, Japan
Wed. Sep 27, 2017 11:15 AM - 12:00 PM Room C1 (1F)

(Wed. Sep 27, 2017 11:15 AM - 12:00 PM Room C1)

[O27-2-2] Mechanistic pharmacodynamic analysis on safety profiles of eribulin in patients with breast cancer using data obtained by post-marketing observational study

Takahisa Kawamura[1], Hidefumi Kasai[2], Valentina Fermanelli[3], Toshiaki Takahashi[4], Yukinori Sakata[5], Toshiyuki Matsuoka[6], Mika Ishii[7], Yusuke Tanigawara[8] (1.Shizuoka Cancer Center, 2.Certara G.K., 3.Keio University School of Medicine, 4.Shizuoka Cancer Center, 5.Eisai Co. Ltd, 6.Eisai Co. Ltd., 7.Eisai Co. Ltd, 8.Keio University School of Medicine)

Keywords: Neutropenia, Eribulin, Pharmacodynamics

Background

Japanese regulation imposes a mandatory post-marketing observational cohort study for new chemical entities and biological products. The primary purpose is collection of safety data in actual clinical settings by an active surveillance approach. In this study, we utilized the observational safety data of eribulin for model-based pharmacodynamic analysis to investigate more detailed safety profile of eribulin in patients with recurrent or metastatic breast cancer (RBC/MBC).

Methods

The demographics and safety data were collected from RBC/MBC patients who were treated with eribulin by an active surveillance method. Since dose-limiting toxicity of eribulin is neutropenia, we analyzed the time course of neutrophil counts using a mechanistic pharmacodynamic model. Plasma concentrations of eribulin were simulated by a population pharmacokinetic model developed by Majid et al. (J. Clin. Pharmacol. 2014). All analyses were performed by Phoenix NLME 7.0 (Certara). Estimated pharmacodynamic parameters were mean transit time (MTT [h]), proliferation rate constant of neutrophils (Kprol [1/h]), elimination rate constant of neutrophils (Kout [1/h]), feedback constant (Gamma) and linear coefficient of drug effect (Slope [mL/ng]).

Results

Clinical and laboratory data of 607 patients who were not given granulocyte colony stimulating factor were collected from July through December 2011. Among them, 401 patients with a total of 5199 neutrophil count measurements were eligible for pharmacodynamic analysis. The estimated mean parameters for eribulin were: MTT=104.5 [h], Kprol=0.0377 [1/h], Kout=0.0295 [1/h], Gamma=0.203 and Slope=0.0413 [mL/ng]. Pathophysiological factors that can affect severity of neutropenia were investigated by Chi-squared test: serum albumin level and baseline neutrophil count (BNEU) were supposed to influence progenitor cells (albumin on Kout/Kprol/MTT and BNEU on Kprol).

Conclusions

The present study reports the first example that observational data collected by a post-marketing cohort study can be successfully applied to a model-based safety analysis. Different from pre-marketing clinical trials which strictly limit the eligible population, the use of post-marketing data is useful to investigate extensive safety profiles of eribulin in patients with broader backgrounds. The obtained safety profile of real-world clinical settings will provide clinically useful information for the treatment of breast cancer using eribulin.