새로운 항암제의 골수억제양상에 대한 약동/약력학적 모델

이소영, 배균섭, 조주연, 임형석, 정재용, 홍경섭, 장인진, 신상구

서울대학교 의과대학 약리학교실, 서울대학교병원 임상의학연구소 임상시험센터

Pharmacokinetic/ Pharmacodynamic Model for the Time Course of Myelosuppression of New Anticancer Drug

So-Young Yi, Kyun-Seop Bae, MD, Joo-Youn Cho, PhD, Hyeong-Seok Lim, MD, Jae-Yong Chung, MD, Kyoung-Sup Hong, MD, In-Jin Jang, MD, PhD, Sang-Goo Shin, MD, PhD

Department of Pharmacology and Clinical Trial Center/Clinical Research Institute, Seoul National University College of Medicine and Hospital, Seoul, Korea

CKD-602 (7-[2-(N-isopropylamino)ethyl]-(20S)-camptothecin), a new derivative of camptothecin, is a topoisomerase I inhibitor that has shown antitumor activity in many tumors. Because the major dose-limiting toxicity of CKD-602 was the myelosuppression, particularly neutropenia, a PD model describing the entire time course of myelosuppression is valuable.

CKD-602 at doses ranging from 0.5 to 0.9 mg/m^2/d were infused for 30 minutes on 5 consecutive days every 3 weeks to patients with advanced solid malignancies. PK analysis was performed using 26 blood samples per patient on days 1 and 5 in 12 patients of a phase I study and 2 blood samples per patient in 6 patients of a phase II study. Complete blood counts for myelosuppression model were measured once a week or more until recovery in 18 patients of phase I/II study.

The PK of CKD-602 was best described using a 3 compartments model. The derived PK parameters were used in the AUC-dependent PD model, which had 4 compartments corresponding to two mitotic compartments of bone marrow, one maturation-storage compartment of bone marrow, and one peripheral blood compartment. Each baseline value of neutrophils, leukocytes, and platelets was used as the covariate of the rate constant in the mitotic compartment.

This mechanistic model successfully related the systemic exposure to CKD-602 to the entire time course of myelosuppression using both PK study data and limited sampling data.