Factors for Hematopoietic Toxicity of Carboplatin: Refining the Targeting of Carboplatin Systemic Exposure

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Résumé en anglais	Purpose Area under the curve (AUC) dosing is routinely carried out for carboplatin, but the chosen target AUC values remain largely empirical. This multicenter pharmacokinetic-pharmacodynamic (PK-PD) study was performed to determine the covariates involved in the interindividual variability of carboplatin hematotoxicity that should be considered when choosing individual target AUCs.Patients and Methods Three hundred eighty-three patients received carboplatin as part of established regimens. A semi-physiologic population PK-PD model was applied to describe separately the time course of absolute neutrophil and platelet counts using NONMEM software. The plasma ultrafiltrable carboplatin concentration (CCarbo) was assumed to inhibit the proliferation of blood cell precursors through a linear model: drug effect = slope × CCarbo. The slope corresponds to the patients' sensitivity to carboplatin hematotoxicity. The relationships between the patients' sensitivity to the neutropenic or thrombopenic effects of carboplatin and various covariates, including associated chemotherapies, demographic, biologic, and pharmacogenetic data, were studied. Results The sensitivity of carboplatin-induced thrombocytopenia decreased in the case of concomitant paclitaxel chemotherapy (slope decreased by 24%), whereas it increased with coadministration of etoposide and gemcitabine (slope increased by 45% and 133%, respectively). For neutropenia, the sensitivity increased when carboplatin was combined with other cytotoxics (slope increased by 76%). Conclusion This study provides useful information to clinicians to better estimate the hematopoietic toxicity of carboplatin and thus choose more rationally carboplatin target AUCs as a function of pretreatment or concomitantly administered chemotherapies. For example, an AUC of 5 mg/mL · min is associated with a risk of grade 3 or 4 thrombocytopenia of 2% in combination with paclitaxel versus 38% with gemcitabine in a non-pretreated patient.
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