Katarina VUČIĆEVIĆ

DEPARTMENT OF PHARMACOKINETICS AND CLINICAL PHARMACY, FACULTY OF PHARMACY – UNIVERSITYOFBELGRADE, VOJVODE STEPE 450, 11221 BELGRADE, REPUBLIC OF SERBIA

The importance of pembrolizumab and nivolumab pharmacokinetics in the treatment of oncology patients

Key words: disposition, variability, PK-PDrelationship, monoclonal antibody.

The use of monoclonal antibodies (mAt) in the treatment of oncology patientshas expanded significantly in the last 5 years, as clinical studies and practice have confirmed better treatment outcomes and longer survival with less toxicity,at the same time. All currently registered drugs have the same basic structure, which corresponds to immunoglobulin G (IgG). mAt acting as inhibitors of immune checkpoint inhibitors (ICI), such as pembrolizumab and nivolumab, significantly improved the prognosis of patients with melanoma, non-small cell lung carcinoma, classical Hodgkin's lymphoma and other malignancies. Pembrolizumab is a potent, highly selective, IgG4-kappa humanized mAt, while nivolumab is a human IgG4. Both drugs prevent the interaction of programmed cell death (PD-1) and its ligands (PD-L1 and PD-L2). Understanding the pharmacokinetic profile of the drug as well as its association with the efficacy and safety profileis necessary.

High interindividual pharmacokinetic variability of mAt ICI (>30%) was observed in the clinical studies, and it is only partially described using demographic and individual clinical characteristics of patients. Both drugs are administeredvia a 30-minute intravenous infusion,hence their bioavailability is complete. Dosing regimen of these drugs is largely dependent on the tumor type. Therefore, doses of pembrolizumabare 2 mg/kg or 200 mg every 3 weeks, whilenivolumabis administered at doses of 3 mg/kg, 240 mg or 480 mg every 2-4 weeks. The pharmacokinetic behavior of mAtconsiderably differs from the chemical drugs.In general,mAt have a low volume distribution due to limited distribution in the extracellular area (volumen of the central compartment is about 3.5 L, while the peripheral 3-4 L), a long half-life (approximately 25-27 days), and the target receptor-mediated disposition with dose and/or time-dependent and independent clearance. The average clearance of pembrolizumab is 0.168-0.249 L/day, whilenivolumab'sis about 0.36 L/day. Significant interindividual(about 35%) and interoccasionalvariability during the treatment(25%) in the clearance has been identifiedfor these drugs. They are primarily metabolized by degradation to smaller peptides and amino acids in many tissues of the organism,similarly as endogenous Ig. In order to establish exposure-efficacy relationship, so far,different parameters have shown a satisfactory correlation. Thus, minimum, average concentrations in the steady-state and clearance are correlated with one of the following parameters: response to therapy (partial or complete), overall survival, reduction of tumor size.

Since pembrolizumab and nivolumab are relatively novel drugs, there is still insufficient data and evidences on the possibilities to individualize therapy, taking into account the individual pharmacokinetic profile of the drugs. Therefore, the purpose of this lecture is to provide insight into pharmacokinetics and pharmacokinetic variability of pembrolizumab and nivolumab, and the relationship with the efficacy of the drugs.

Monika SONC

INSTITUTE OF ONCOLOGY LJUBLJANA, SLOVENIA

Pharmacovigilance: Monitoring of the Adverse Drug Reactions

At the Institute of Oncology Ljubljana monitoring, recording and reporting ofadverse drug reactionsis particularly importantbecausea lotof new drugs are used in cancer treatment. Evenafter thedrugreceivesmarketing authorizationand can be usedin