Impact of single-nucleotide variants and nutritional status on population pharmacokinetics of Doxorubicin, and its effect on cardiotoxicity in children with leukemia

Abstract

Purpose: Doxorubicin is an important antineoplastic agent with wide interindividual variability in response to treatment GQ5 and in its cardiotoxic effects. To determine the effect of genotypic status of three single-nucleotide variants in ABCC1, NCF4, and CBR3 genes and nutritional status assessed by body mass index, on the population pharmacokinetics of Doxorubicin and its cardiotoxic effects in pediatric patients with leukemia.

Patients and methods: Seventy pediatric patients treated with Doxorubicin were studied, in which 189 biological sam- ples were obtained to determine Doxorubicin concentrations (1 to 3 samples per patient) at different times, for 20 h. Results: Low body mass index and age ≤ 7 years were associated with decreased clearance of Doxorubicin, and female gender was associated with increased clearance of Doxorubicin. Low BMI and low height were associated with a decrease

and increase, respectively, in the intercompartmental clearance (Q) of Doxorubicin. TT homozygosity of the single- nucleotide variant rs3743527 of the ABCC1 gene was associated with an increase in clearance and decreased area under the curve, AA homozygosity of the single-nucleotide variant rs1883112 of the NCF4 gene was associated with a decrease in the volume of distribution in the peripheral compartment (V2), and GG homozygosity of CBR3 rs1056892 with increasing area under the curve.

Conclusion: Some covariates studied are directly related to the increase or decrease of the pharmacokinetic parameters of Doxorubicin. Decreased clearance, V2, and increased area under the curve were associated with systolic dysfunction, and decreased Q and V2 were associated with diastolic dysfunction. These results may contribute to the effective and safe use of Doxorubicin in pediatric patients with leukemia.