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

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Abstract

Doxorubicin (DOX) is a highly useful antineoplastic in the treatment of different types of cancer; however, its use is limited due to its wide variability between patients in their susceptibility to the cardiotoxic effects of anthracyclines. **Purpose:** The aim of this study was to determine the effect of single nucleotide variants (SNV) and the nutritional status on the population pharmacokinetics of DOX, and their repercussions on cardiotoxicity in pediatric patients with leukemia. **Patients and methods:** Seventy pediatric patients treated with DOX were studied, in whom 189 biological samples (1 to 3 samples per patient) were obtained at different random times, for 20 hours. **Results:** Body mass index, age [?] 7 years and female sex were associated with a decrease in DOX clearance. Low height was associated with an increase in pharmacokinetics parameters of DOX. The Wild type (WT) genotype of *ABCC1* rs3743527 variant was associated with an increase in clearance (CL), and the homozygous variant (HV) genotype of *NCF4* rs1883112 SNV was associated with a decrease in peripheral compartment (V2) of the peripheral compartment. **Conclusion:** The SNV of the *ABCC1* and *NCF4* genes influence the increase and decrease in DOX CL, in addition, characteristics such as sex and height were associated with the decrease and increase in DOX CL respectively. The pharmacokinetic parameters show an influence on the development of cardiotoxicity by DOX. The decrease in CL and V2 were associated with systolic disfunction. The decrease in the intercompartmental clearance (Q) and in the volume distribution (V2) were associated with diastolic disfunction. In clinical practice, these results may contribute to the effective and safe use of DOX in pediatric cancer patients.

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