Measurement of deferasirox plasma concentrations in pediatric hematopoietic stem cell transplantation patients with iron overload. Is it useful the application in clinical practice?

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Iron overload has been associated with a poor prognosis for patients who undergo to allogeneic hematopoietic stem cell transplantation (HSCT). Iron-chelating therapy improves HSCT outcomes but, in pediatric setting, the knowledge regarding the effects of chelation are lacking. Since this particular cohort of patients could show various degrees of hepatic impairment, our study born from the need to understand what is the best therapeutic approach in the use of deferasirox (for chelation therapy). This is an important tool considering that, deferasirox, unlike the iron chelating drugs previously used (i.e. deferoxamine and deferiprone), can be administered once daily orally, improving compliance and discomfort for the patients. As regard as safety, we evaluated the onset of possible toxicity.

We performed a five's year retrospective analysis, in HSCT pediatric patients treated with deferasirox, after transplant. Patient's tissue iron concentration, hematological parameters and the degree of hepatic impairment were documented. Deferasirox plasma concentrations were determined by high performance liquid chromatography assay.

All patients showed iron tissue overload and 92.8% of the 42 patients enrolled showed a various degree of liver damage. The mean deferasirox dose administered was 22,5 mg/Kg/die and the mean duration of treatment was 88.8±82.9 days. The mean minimum steady-state plasma concentrations of deferasirox (DFX-Ctrough) value was 17.4 mcg/mL; 52.4% of patients developed adverse events (AEs) and among these 59.1% of grade 3 or higher; 77.3% interrupted the treatment.

Our preliminary data suggest that the concentration/dose ratio of deferasirox was higher in patients who developed AEs than those who have not developed them and that higher plasma concentrations of the drug seems to be correlated with the degree of severity of hepatic impairment ($p = 0.0044$). Because of the retrospective of the study, we could not assess the participants' genetic characteristic that could be involved in toxicity.

HSCT is associated with considerable morbidity and mortality related to iron overload. To date, few studies have been reported for iron chelation therapy after HSCT. Regardless the efficacy of deferasirox to iron overload, considering that the drug elimination is primarily biliary, it could be hypothesize that in HSCT pediatric patients, in which often occur an hepatic impairment, the plasma concentration of drugs could reach levels that promote the onset of toxicity; hence the need to perform a therapeutic drug monitoring.