INTRODUCTION

Doxorubicin (DOX) is a topoisomerase II inhibitor used in the treatment of several types of cancer, both solid and hematologic. Nevertheless, anticancer treatments have significant side effects, like nephrotoxicity and hepatotoxicity. However, the underlying mechanisms of DOX-induced nephrotoxicity and hepatotoxicity remain largely unknown. Thus, this work aims to assess the nephrotoxicity and hepatotoxicity one week and 5 months after DOX last administration.

EXPERIMENTAL PROTOCOL

Figure 1. Experimental protocol using adult male CD-1 mice. The experimental protocol was approved by the local Animal Welfare Body (ref. 140/2015) and the Portuguese National Authority for Animal Health (ref. 021322 of 2016/10/26). Six intraperitoneal injections were given and following sacrifice, liver and kidneys were removed and analysed (organ weight/brain weight ratio, histology, and ATP levels). Statistical analyses were carried out by the Mann Whitney test.

RESULTS

Figure 2. ATP levels (in mmol) per mg of protein in the kidney of mice euthanized one week after the last administration of DOX (A) and mice euthanized 5 months after the last administration (B). Results are presented as means ± standard deviation (SD). Statistical comparisons were made using the Mann-Whitney test.

Figure 4. Light microscopy renal representative images of control mice (A) and DOX-treated mice (B) sacrificed one week after last administration, and control mice (C) and DOX-treated mice (D) 5 months after the last administration. While control groups presented normal morphology, both DOX-treated groups presented vascular congestion (blue arrow) and inflammatory infiltration (black arrow) in the kidneys.

Figure 5. Light microscopy representative images of the liver of control mice (A) and DOX-treated mice (B) sacrificed one week after last administration, and control mice (C) and DOX-treated mice (D) 5 months after the last administration Control groups presented normal morphology; both DOX-treated groups presented necrotic zones (green arrow) and vacuolization - microvesicular steatosis (red arrow). In addition, DOX-treated and sacrificed one week after the last administration presented inflammatory infiltration (black arrow) and vascular congestion (blue arrow).

In the kidneys and the liver, there was no significant statistically differences in ATP levels between control group and the DOX-treated group in both mice sacrificed one week after the last administration of DOX and sacrificed 5 months after the last administration. Histopathological examination showed that DOX administration caused visible alterations to renal and hepatic tissues, causing damage such as vascular congestion, inflammatory infiltration, necrotic zones and vacuolization. Most of these effects were seen in both DOX-treated mice, however, liver inflammatory infiltration and vascular congestion were only observed one week after the last administration.

Discussion and conclusions

In the kidneys and the liver, there was no significant statistically differences in ATP levels between control group and the DOX-treated group in both mice sacrificed one week after the last administration of DOX and sacrificed 5 months after the last administration. Histopathological examination showed that DOX administration caused visible alterations to renal and hepatic tissues, causing damage such as vascular congestion, inflammatory infiltration, necrotic zones and vacuolization. Most of these effects were seen in both DOX-treated mice, however, liver inflammatory infiltration and vascular congestion were only observed one week after the last administration.

REFERENCES

[1] World Health Organization (WHO); 2020

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