Anticancer drugs-induced toxicity in different age male CD-1 mice

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Introduction

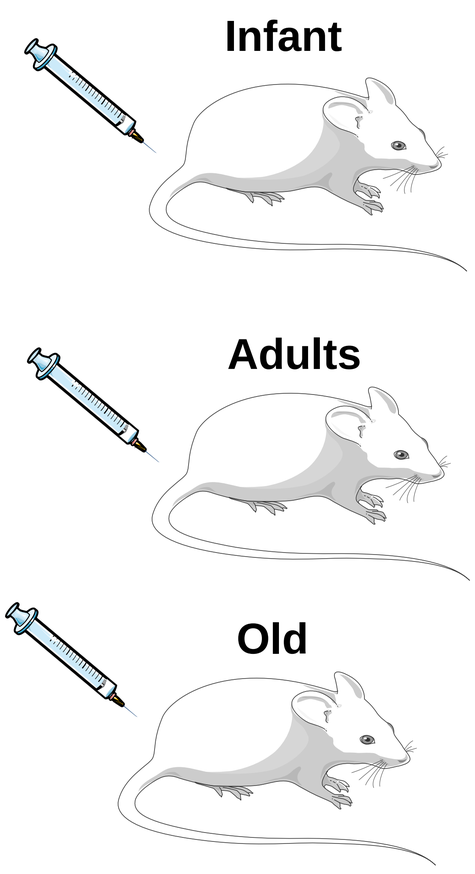
Anticancer drugs like doxorubicin (DOX) and mitoxantrone (MTX) are used to treat cancer. Nevertheless, they have worrying long-term toxicity. MTX and DOX cause cardiotoxicity and several risk factors could aggravate it. The aim of this work was to study the toxicity of clinically relevant MTX and DOX doses in infant (4 weeks), adult (3 months), and old (18-20 months) male CD-1 mice.

Experimental protocol

ADMINISTRATION SCHEDULE:

- 1 mg/ kg of saline (NaCl 0.9%), control group;
- MTX in saline (total cumulative dose of 6mg/kg).
- DOX in saline:
  - first group: infants and adults (total cumulative dose of 18 mg/kg);
  - second group: adults and old (total cumulative dose of 9 mg/kg).

Biweekly intraperitoneal administrations, for 3 weeks were given to all animals.

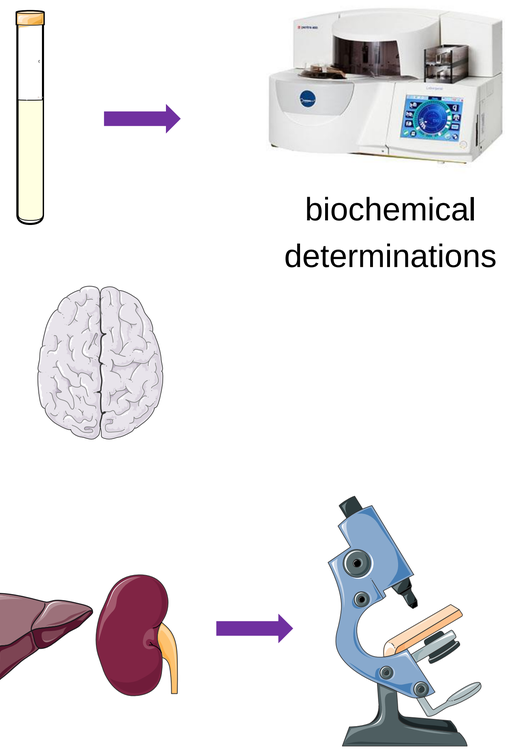


The animals' weight, food and water consumptions and general welfare were recorded throughout the experiment.

sacrificed 17 days after the last injection

sacrificed 7 days after the last injection

The organs were removed and weighted and blood plasma was collected.



biochemical determinations

light microscopy

Results

Regarding the results, **significant body weight loss** was observed in the adult population treated with MTX and DOX 18 mg/kg, and in DOX-treated infants' animals, when compared to the respective controls. In addition, **food and water consumptions decreased** in the infant and adult populations treated with MTX and DOX 18mg/kg. Regarding organ weight/ brain weight ratios at sacrifice, **the ratio of all the organs were significantly decreased** in the MTX and DOX-treated adults, except in adult DOX 9 mg/kg. Alanine aminotransferase (ALT) plasma levels were significantly increased in the MTX and DOX-treated infants. Moreover, in DOX-treated adults (18 mg/kg), aspartate aminotransferase (AST)/ALT ratio and total creatine-kinase (CK) plasma levels increased, when compared to controls. Regarding histology, **all the MTX and DOX-treated populations presented lesions in heart, kidneys, and liver** as did the old control animals. Histological staining using Sirius Red identified a significant increase in interstitial collagen deposition in the myocardium, liver, and kidneys in all drug-treated adult mice.

Discussion and conclusions

Therefore, we can conclude that although cumulative dose is considered a main factor when studying anticancer drugs toxicity, **the age of administration is also determinant in the toxicity** observed. In our study, adult mice seemed to be more prone to MTX and DOX-induced toxicity; still, further data needs to be gathered to determine the underlying factors for that susceptibility.

Acknowledgements

ARM and VMC acknowledge Fundação da Ciência e Tecnologia (FCT) for their grants (SFRH/BD/129359/2017 and SFRH/BPD/110001/2015, respectively). This work is funded by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P., under the Norma Transitória – DL57/2016/CP1334/CT0006. This work was supported by FEDER funds through the Operational Programme for Competitiveness Factors – COMPETE and by national funds by the Fundação para a Ciência e Tecnologia (FCT) within the project "PTDC/DTP-FTO/1489/2014 – POCI01-0145-FEDER-016537".