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CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Contribution ID: **261** Type: **3 - Talk**

Mitochondrial dysfunction: a key player in doxorubicin-induced skeletal and cardiac muscle damage?

Thursday 23 July 2026 16:15 (15 minutes)

Introduction
Anthracyclines are effective treatments for solid and hematological cancers but can cause long-lasting toxicities, including skeletal muscle loss (20–70%) and cardiomyopathy (5–48%). These toxicities contribute to fatigue, reduced physical fitness, and poorer quality of life (QoL), and may limit the use of optimal chemotherapy doses, decreasing the chance of survival. Understanding mechanisms of anthracycline-induced myo- and cardiotoxicity can guide the development of future trials evaluating (non-)pharmacological strategies, such as exercise, to prevent these toxic effects. This pilot study examines changes in skeletal and cardiac muscle mitochondrial function during (R-)CHOP chemotherapy in patients with lymphoma using non-invasive phosphorus (31P) Magnetic Resonance Spectroscopy (MRS).

Methods
Newly diagnosed patients with lymphoma underwent 31P-MRS of the heart and calf muscle before and after completion of chemotherapy. The PCr/γATP ratio in cardiac muscle and the rate constant of PCr recovery following dynamic plantar-flexion exercise in skeletal muscle were evaluated as measures of mitochondrial function. Additionally, fatigue, QoL and physical fitness were assessed. Linear regression models were performed to assess changes over time.

Results
To date, 12 patients have been enrolled, with 4 patients of whom all scans have been completed and analyzed (mean age = 48.8±19.7 years). The PCr/γATP ratio (-0.45, 95% CI -0.81; -0.13) and PCr recovery rate constant (-0.51 s-1, 95% CI -0.89; -0.13) decreased significantly over time. All other outcomes also demonstrated deterioration over the course of chemotherapy. At the conference, data of all 12 patients will be presented.

Conclusion This pilot study demonstrates the ability to monitor skeletal and cardiac muscle mitochondrial damage using 31P-MRS and provides mechanistic evidence for the role of mitochondria in anthracycline-induced myo- and cardiotoxicity. This informs the design of future randomized controlled trials, which aim to investigate effects of (non-)pharmacological treatment options, including exercise, to mitigate these detrimental toxicities.

Keywords

Mitochondrial dysfunction; Chemotherapy; Muscle damage; Exercise

Conflict of Interest & Ethical Approval

yes

Abstract submitters declaration

yes

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Session Classification: Oral Session