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EDITORIAL COMMENT

Of mice and man

Ratos e Homens

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Cisplatin-based chemotherapy is widely used in the treatment of various solid tumors, including ovarian, lung, bladder, and testicular cancers. The anticancer property of cisplatin is not completely understood. Increasing evidence indicates that the pathophysiological mechanisms are multifaceted, involving oxidative stress, DNA damage, alterations in signaling pathways, and direct myocardial damage.[1,2]

Despite its effectiveness, cisplatin-based chemotherapy can have significant side effects. It is known to be nephrotoxic, neurotoxic, and ototoxic. Additionally, less common cardiovascular issues such as high blood pressure, high cholesterol, autonomic dysfunction, arrhythmias and heart failure have been associated with cisplatin treatment. These side effects can occur during treatment or even years later and are not always dose-dependent.

Cisplatin-induced cardiotoxicity can impact the dosage and duration of chemotherapy, which can affect the overall outcome of cancer treatment. During cisplatin infusion, cardiovascular adverse effects can manifest as palpitations, chest pain, and elevated cardiac biomarkers, resembling a myocardial infarction. Vascular damage, platelet aggregation, and enhanced thromboxane formation are believed to contribute to these adverse cardiac effects.[3]

It is worth noting that cisplatin-induced cardiovascular effects can also manifest later in a patient's life. This delayed toxicity is believed to be associated with the long-term presence of cisplatin in the bloodstream, as studies have shown that cisplatin can still be detected in the blood even after 20 years of treatment. This extended exposure to cisplatin can result in elevated levels of endothelial and inflammatory markers in the plasma, potentially leading to direct severe endothelial dysfunction and atherosclerosis and indirectly induced hormonal and metabolic changes.[4]

While cisplatin-based chemotherapy has significantly improved the cure rate of germ cell tumors to 95%, there is a 25-year risk of cardiovascular toxicity in 16% of patients.[5–7] Delayed cardiovascular toxicity such as acute myocardial infarction and cerebrovascular events is reported by Chaudhary et al.[8] A study specifically designed to assess the development of cardiovascular risk factors in patients cured of testicular cancer treated with cisplatin reported elevated LDL and cholesterol levels, depleted HDL levels and increased body mass index in 28% of patients at 4–6 years.[9]

The autonomic nervous system (ANS) plays a crucial role in regulating cardiovascular function, including heart rate, blood pressure, and vasomotor tone.

Dysregulation of the ANS chemo- and radiotherapy-induced affects approximately 80% of cancer patients and is particularly found in platinum-based therapy. It is closely related to an increased risk of cardiovascular complications, such as arrhythmias, hypertension, and heart failure.[10]

Several pharmacological strategies have been investigated to shield the heart against the harmful impacts of chemotherapy on cardiac health. Monitoring and adjusting electrolyte levels, managing blood pressure, monitoring ECG, and considering dose modifications or alternative treatments for high-risk individuals are all approaches that have been explored. Preventive measures and early intervention are crucial in addressing cardiotoxicity, including

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conducting baseline cardiovascular evaluations, managing cardiovascular risk factors, and making lifestyle modifications all contribute to reducing cardiac risks.

Regular aerobic exercise has been shown to improve ANS function and cardiovascular health in various populations, including those with cardiovascular disease. It is possible that exercise may also be beneficial for cancer patients undergoing chemotherapy, by improving ANS function and reducing the risk of cardiovascular complications.

Future research is needed to better understand the mechanisms underlying cisplatin chemotherapy-induced cardiovascular dysfunction and to determine the optimal exercise interventions for these patients. In the meantime, encouraging cancer patients to engage in regular aerobic exercise, under the guidance of healthcare providers, may help to attenuate the negative effects of chemotherapy on the cardiovascular system.[11]

Mouse models are commonly used to study cisplatin's effects, as mice respond similarly to humans. Mice develop all cisplatin side effects in a dose- and time-dependent manner. Just like humans, mice also develop cisplatin side effects of varying severity from mild to multi-organ failure, each disease has its own course and pathophysiological response or molecular signature. Despite all the similarities, there is an apparent gap between the results in animal models and human clinical trials.[12,13]

The study by Santos et al.,[14] investigated the potential benefits of physical exercise in mitigating the cardiotoxic effects of cisplatin. In the study, mice were treated with cisplatin to induce electrocardiogram (ECG) changes and then subjected to moderate-intensity physical exercise on a treadmill.

The results of the study showed that moderate-intensity physical exercise attenuated the cisplatin-induced ECG changes. More specifically, the exercise group showed improvements in various ECG parameters, such as heart rate variability and QT interval duration, compared to the sedentary group.

These findings suggest that moderate-intensity physical exercise may have a protective effect on the heart and help counteract the cardiotoxic effects of cisplatin. Further research is needed to fully understand the mechanisms underlying this protective effect and to optimize exercise strategies for cancer patients undergoing cisplatin treatment.

In another study[15] from the same group, the authors investigated the effect of physical exercise and pyridostigmine treatment on gastrointestinal and cardiovascular changes in cisplatin-treated male Wistar rats. They concluded that physical exercise and pyridostigmine treatment contribute to the attenuation of the effects of cisplatin on the gastrointestinal tract and cardiovascular system, with decreased sympathetic tone and increased parasympathetic tone, causing an improvement in autonomic dysfunction in rats.

These studies were conducted in tumor-free mice, so we do not know what the results would be if they were carried out in a tumor environment. Nonetheless, the present study shows that these interventions could potentially be beneficial in clinical settings for patients undergoing cisplatin treatment, although further research is needed to confirm these effects in humans.

Nonetheless, incorporating regular physical activity into cancer treatment regimens, as recommended in the guidelines, may be a promising approach to improving cardiovascular health and overall well-being in cancer patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Rachma B, Savitri M, Sutanto H. Cardiotoxicity in platinum-based chemotherapy: mechanisms, manifestations, and management. Cancer Pathogen Ther. 2024 [consultado 25 Apr 2024], http://dx.doi.org/10.1016/j.cpt.2024.04.004.
2. Bano N, Najam R, Qazi F. Adverse cardiovascular manifestations of cisplatin: a review. Int J Pharm Sci Rev Res. 2013;18:80–5.
3. Herradón E, González C, Uranga JA, et al. Characterization of cardiovascular alterations induced by different chronic cisplatin treatments. Front Pharmacol. 2017;8:196.
4. Dugbartey GJ, Peppone LJ, de Graaf IAM. An integrative view of cisplatin-induced renal and cardiac toxicities: molecular mechanisms, current treatment challenges and potential protective measures. Toxicology. 2016;371:58–66.
5. Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. Clin Oncol. 2000;18:1725–32.
6. Feldman DR, Schaffer WL, Steingart RM. Late cardiovascular toxicity following chemotherapy for germ cell tumors. J Natl Compr Canc Netw. 2012;10:537–44.
7. Eftsathiou E, Logothetis CJ. Review of late complications of treatment and late relapse in testicular cancer. J Natl Compr Canc Netw. 2006;4:1059–70.
8. Chaudhary UB, Haldas JR. Long-term complications of chemotherapy for germ cell tumours. Drugs. 2003;63:1565–77.
9. Gietema JA, Sleijfer DT, Willemse PH, et al. Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated non seminomatous testicular cancer. Ann Intern Med. 1992;116:709–15.
10. Adams SC, Schondorf R, Benoit J, et al. Impact of cancer and chemotherapy on autonomic nervous system function and cardiovascular reactivity in young adults with cancer: a case-controlled feasibility study. BMC Cancer. 2015;15:414.
11. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J. 2022;43:4229–361.
12. Hojman P, Fjelbye J, Zerahn B, et al. Voluntary exercise prevents cisplatin-induced muscle wasting during chemotherapy in mice. PLoS One. 2014;9, e109030.
13. Perše M. Cisplatin mouse models: treatment, toxicity and translatability. Biomedicines. 2021;9:1406.
14. Silva MS, Rocha CHL, Santos AAD, et al. Moderately intense physical exercise alleviates electrocardiographic changes induced by cisplatin in rats. Rev Port Cardiol. 2024, http://dx.doi.org/10.1016/j.repc.2024.03.006.
15. Silva MS, Gomes YA, Cavalcante MLS, et al. Exercise and pyridostigmine prevents gastric emptying delay and increase blood pressure and cisplatin-induced baroreflex sensitivity in rats. Life Sci. 2021;267, 118972.