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EDITORIAL COMMENT

Anthracycline-Induced Vascular Dysfunction

Is MitoQ the Answer?*

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Anthracycline antibiotics have been in use for more than half a century in the treatment of cancer and the dose-limiting cardiovascular toxicity has been recognized for most of that time. Despite this and other toxicities, anthracyclines continue to be important components of chemotherapy for both solid and hematologic malignancies. There has been a great deal of effort put into understanding the mechanisms for the cardiovascular toxicity of anthracyclines and development of strategies to limit the adverse effects, while not interfering with the antitumor efficacy. Preclinical models have been used extensively, and many rodents have been sacrificed in the hopes of making anthracyclines a safer class of medications for humans. Clayton et al. (1) have added to that effort and in an elegant set of experiments advance the concept that protection of vasculature with repletion of mitochondrial coenzyme Q10 could be the answer to this age-old question.

The effects of anthracyclines on mitochondrial function with increased generation of oxidant stress are well established, including the effect on mitochondrial coenzyme Q10 synthesis (2). This has led to clinical studies examining whether coenzyme Q10 repletion can prevent cardiotoxicity (3). What is novel in the work from Clayton et al. (1) is the use of modified coenzyme Q10 that is predominantly taken up into mitochondria – "MitoQ." Using this orally bioavailable, over-the-counter antioxidant, they show that the endothelium-dependent vasodilation of carotid arteries is protected in mice treated with a single high dose of doxorubicin. Noting a drop in the levels of vascular endothelial growth factor A (VEGF-A), the investigators advance the hypothesis that doxorubicin disruption of endothelial VEGF could be central to the effects of doxorubicin on arterial function.

Preclinical experiments and clinical studies looking to understand and prevent anthracycline-associated cardiovascular dysfunction abound, and it is worth considering how the current study jives with the rest of this literature. Anthracyclines are used clinically in multiple distinct dosing schedules, and the significance of preclinical studies should be considered in this context. In the current experimental protocol, Clayton et al. (1) use a single high-dose exposure, similar to induction chemotherapy in the treatment of some hematologic malignancies, and different from the multiple cycles of anthracycline-based chemotherapy used in solid tumors such as breast cancer. In this context, it is notable that childhood survivors of hematologic malignancies treated with anthracycline-based chemotherapy do show signs of persistent impaired vascular endothelial function (4). In contrast, these same changes do not persist in adult breast cancer survivors who received a series of lower-dose exposure to anthracyclines (5). This clinical literature suggests that the findings by Clayton et al. (1) may be most translatable to a subset of anthracycline-treated patients.

With regards to mechanistic insights suggesting disrupted VEGF-A as a mediator of the vascular

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dysfunction, some clinical data does not support that hypothesis. The effect of anthracyclines on circulating VEGF-A and other cardiovascular growth factors has been examined in samples collected from children undergoing anthracycline-based chemotherapy. Plasma levels of VEGF-A increased after anthracycline treatment in contrast to what was seen in this mouse studies of Clayton et al. (1,6). In contrast, the cardiovascular growth factors neuregulin (NRG) and cardiotrophin-1 decreased after anthracycline treatment in these same children (6). The decrease in NRG after anthracyclines has also been observed in adults undergoing anthracycline-based chemotherapy, which is interpretable as a sign of vascular endothelial cell injury (7). Endothelial cell-derived NRG acts through the ERBB receptor tyrosine kinase family to regulate the growth and survival of cardiac myocytes, and protects from anthracycline cardiac cytotoxicity (8,9). Given the interaction between VEGF-A and NRG in regulating the adaptation of the cardiovascular system to stress and the clinical data showing anthracycline-associated decline in plasma NRG, further work should be considered (10).

Perhaps the trickiest part of interpreting the work by Clayton et al. (1) is when answering questions from patients anticipating anthracycline-based treatment. MitoQ and other coenzyme Q10 preparations are available over the counter, and coenzyme Q10 supplementation has been studied not only as a way to limit injury to the cardiovascular system, but also kidney and reproductive organs (11,12). These promising preclinical results may lead people to self-medicate during their cancer treatment. As Clayton et al. (1) acknowledge, that would be a bad idea. They acknowledge that the National Cancer Institute guidelines specifically warn against taking antioxidants concurrent with chemotherapy. In fact coenzyme Q10 was among a group of dietary supplements that was associated with worse outcomes in people being treated for breast cancer (13). So, unless a definitive clinical study is conducted showing a beneficial effect of MitoQ in this clinical setting, it seems the best advice we can currently give is to leave the MitoQ on the shelf.

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