



Florida
CHAPTER



Anthracycline Cardio-Toxicity: The calm before the storm

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CANCER BACKGROUND

Cancer therapy with ANTHRACYCLINES began in the late 60's when daunorubicin was discovered. It is produced naturally by *Streptomyces peucetius*, a bacteria found in soil. Clinically the most important anthracyclines are doxorubicin, daunorubicin, epirubicin and idarubicin, and have a wide range of therapeutic activity in most solid and hematologic malignancies. They are considered the prototype for CTCT (Cancer Treatment Cardiac-toxicity).

ADVERSE EFFECTS

Adverse effects are due to the mechanism of action related to topoisomerase II inhibition, which occurs as a result of anthracycline intercalation between adjacent DNA base pairs. This results in activation of programmed death pathways. Production of hydroxyl free radicals is associated with both anti-tumor and cardiac toxicity. Myocardial tissue is particularly susceptible to free radical damage.

Life threatening arrhythmia within hours of infusion or any time during therapy

EKG changes: cardiogenic shock

The risk of myopathy increases with increasing doses, (65% at cumulative dose of 550mg/m²) but there is no safe dose, and toxicity can occur at any dose (incidence rates 1-20%); more

likely with other risk factors for heart disease (older age, prior heart disease, HTN, DM, known PVD, HLD).

RECOMMENDATIONS

Baseline assessment of left ventricular function by echocardiography, 2-D, 3-D and global strain, with use of cardiac MRI or MUGA scans in selected patients. Repeat imaging after 240 mg/m², and 6 months after termination of therapy. There is no consensus on frequency of imaging in long term follow up.

The drug dexrazoxane provides some protection against anthracycline-induced cardiomyopathy by preventing iron -based oxidative stress and inhibiting topoisomerase 2 b, but there is concern of mitigating cancer effectiveness (still an area of debate) as well as increasing secondary malignancies in childhood survivors. The literature supports low dose carvedilol, and ACE-I/ARB, and possibly statins for primary prevention in high risk patients.

DATA TO SUPPORT

Anthracycline Cardio-Toxicity spans decades:

Gilladoga AC, Manuel C, Tan CT. et al. The cardiotoxicity of adriamycin and daunomycin in children. *Cancer*. 1976 Feb;37(2 Suppl):1070-8.

Kheiri B, Abdalla A, Osman M et al.

Meta-Analysis of carvedilol for the prevention of Anthracycline-Induced Cardiotoxicity. *Am J Cardiol* 2018;122:1959-64.

Society Guidelines: Canadian Cardiology Society guidelines for evaluation and management of Cardiovascular Complications of Cancer Therapy. *Canadian J Cardiology*. 2016: 32; 831-841.

INDICATIONS

Indications for use are fairly common, and because there are so many applications, Cardiologists and Oncologists need to be watchful for side effects that can occur both early and late. There is no safe dose and cardiotoxicity can be amplified in patients who also receive radiation therapy (XRT) or HER-2 therapies. Preventive strategies are still evolving.

ONCOLOGY COMMENTS

Anthracycline based therapy in diseases with a poor prognosis are treated differently. The risk vs benefit ratio is altered in these cases to



Anthracycline *continued*

favor treatment. In a good prognostic disease such as breast cancer, cardiotoxicity is a much more important issue as they are expected to survive their cancer.

In a number of studies, symptomatic or asymptomatic cardiac dysfunction was observed in 27% of patients who received concomitant anthracycline and trastuzumab therapy. The rate of cardiac events was much lower in patients given trastuzumab alone (4.7%), leading to the recommendation to separate therapies. www.cancernetwork.com/breast-cancer/anthracycline-cardiotoxicity-after-breast-cancer-treatment/page/0/1

Monitoring after therapy (usually with 2-D echocardiography) is recommended after 6 months, 1-2 years and probably after 5 years. There is controversy on frequency of testing for long term follow up and should be adjusted to patient's individual risk.

Not everyone who gets anthracycline must have a cardio-oncology consult, however, those with pre-existing heart disease, or those with traditional risk factors for heart disease need to be aggressively treated and monitored for heart disease. This can be done by the PCP, or if they prefer, then Cardio-Oncology should be involved.