Individualised prevention of anthracycline-induced cardiotoxicity in cancer treatment

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**Abstract**

Anthracycline antibiotics are highly effective antineoplastic drugs used in a wide range of cancers, however they can have adverse effects on the heart. Depending on the needed dosage and presence of certain gene variants that may influence risk, use of cardiotoxic analogs, ACE-inhibitors and cardioprotective drugs may help to individualise treatment to prevent cardiotoxic risk.

**Background**

Anthracycline use may, years after treatment, cause cardiomyopathy where the heart does not pump efficiently and congestive heart failure may ensue. Potentially irreversible dilated cardiomyopathy may occur (1). In animal models of anthracycline cardiotoxicity, irreversible mitochondrial impairment, in part related to free-radical injury during therapy, resulting in late cardiomyopathy was found. Long-term survivors of childhood cancer have a greater than 8-fold increased risk of CV mortality compared to a healthy population 25 years after therapy. This risk increases progressively over time and appears related in part to anthracycline chemotherapy. Anthracycline-induced cardiotoxicity in long-term survivors of childhood cancer is characterised by reduced left ventricular wall thickness and mass, which is indicative of decreased cardiac muscle and depressed left ventricular contractility, signs of an unhealthy heart muscle (2). The cardiotoxic risk increases with the high cumulative anthracycline doses, anthracycline dose intensity, and radiotherapy, which, in patients with cancer treated with anthracyclines, can exacerbate anthracycline-induced cardiac tissue damage.

**Higher doses provoke higher cardiotoxic risk, however genes play a role**

While some patients with little exposure have considerable cardiac damage others with higher exposure don't develop heart problems. Inter-individual variability in tolerance to (and efficacy of) cumulative anthracycline exposure has indicated a role for genetic susceptibility with this drug. It has been hypothesised that variations in genes with a function in doxorubicin pharmacology, (an anthracycline) may contribute to variation in doxorubicin toxicity (3). Evidence suggests that genetic variants affect the expression of proteins associated with the transport, metabolism and mechanism of action of doxorubicin, and may influence efficacy and toxicity (4). For example, single nucleotide polymorphisms (SNPs) in the ABCB1 transporter gene have been shown to influence both pharmacokinetics and outcome following doxorubicin chemotherapy. Similar associations have been described for SNPs in the carbonyl reductase (CRB1 and CRB3) genes: variants in the CBR1 and CBR3 genes are known to affect the enzyme's activity, and it has
been hypothesised that cardiotoxic risk is increased among those who received low doses of anthracyclines if they carry these particular genetic variants (5).

CBRs are enzymes that help metabolise anthracyclines into highly cardiotoxic C-13 alcohol metabolites (doxorubicin and daunorubicin into the cardiotoxic metabolites doxorubicinol and daunorubicinol), which are substances that can damage the heart: the CBR1 gene variant increased the risk of heart problems by more than five-fold, and the CBR3 gene variant increased the risk by more than three-fold. Multivariate analysis adjusted for age at diagnosis, gender, radiation to the heart, race/ethnicity, years of diagnosis, primary diagnosis, and follow-up showed that compared with with no anthracycline exposure, the risk of cardiomyopathy in those exposed to anthracyclines was: 2.02-fold higher at 1 to 100 mg/m²; 3.56-fold at 101 to 200 mg/m²; 11.43-fold at 201 to 300 mg/m²; 22.32-fold at 301 mg/m² and higher.

Patients with acute lymphoblastic leukaemia or non-Hodgkin's lymphoma are typically given lower doses of anthracyclines. However those with bone tumours, sarcomas, and acute myeloid leukaemia typically receive higher doses of anthracyclines, and therefore face an increased risk of cardiomyopathy regardless of gene status (6).

**Preventing effects of cardiotoxic risk**

Patients who are found to have this specific gene variant could be offered an alternative noncardiotoxic chemotherapy or, if anthracyclines were still considered necessary, may benefit from aggressive surveillance and/or cardioprotection with cardioprotective agents. This would be an example of personalised medicine and an important step toward safer treatment of cancer patients (7).

Attempts to reduce anthracycline cardiotoxicity have been directed towards:

1. Decreasing myocardial concentrations of anthracyclines and their metabolites by dose limitation and schedule modification, to avoid anthracycline peak levels which may reduce the pathologic and clinical cardiotoxicity - although this has not always been observed.
2. Cardiotoxic analogs, such as liposomal anthracyclines, are a new class of agents that may allow more specific organ targeting, thereby producing less systemic and cardiac toxicity. More studies, however, are required to assess the advantages, if any, of these preparations over classical anthracyclines.
3. Angiotensin-converting enzyme inhibitors; Several studies have shown that cardiomyopathy disease progression can be delayed in adults by using ACE-inhibitors. Studies in long-term survivors of pediatric cancer showed significant benefits in preventing cardiac functional deterioration on a short-term basis, but this is not sustained (8).
4. Concurrently administering a cardioprotective agent.
5. A) The cardioprotective agent, dexrazoxane, an iron chelator, is highly effective and significantly reduces the cardiotoxicity associated with the anthracyclines daunorubicin, doxorubicin, and epirubicin, provides short-term cardioprotection to most patients receiving even the most intensive doxorubicin-containing regimens, has no effect on the event-free survival rate at 2.5 years, which emphasises the fact that it does not detrimentally affect the efficacy of anthracycline therapy. Its long-term benefits remain to be determined, and data remain insufficient to make specific recommendations regarding current use of dexrazoxane (9).
   
   B) Experimental studies showed that the cardioprotectant flavonoid 7-mono hydroxyethyl
rutoside (cardioprotectant monoHER) inhibits CBR1 activity. CBR1 V88I genotype status and the type of anthracycline substrate dictate the inhibition of CBR1 activity. MonoHER acted as a competitive CBR1 inhibitor when using daunorubicin as a substrate, acted as an uncompetitive CBR1 inhibitor for the small quinone substrate menadione (10).

**Conclusion** Significant inter-individual variability in tolerance to cumulative anthracycline exposure has indicated a role for genetic susceptibility. A large number of genetic polymorphisms have been reported in the genes that mediate the metabolism, transport and pharmacological activity of doxorubicin. The clinical significance of these findings is still undergoing evaluation, but it has been hypothesised that a personalised treatment of cancer may be needed.

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**References**


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