

# ANTHRACYCLINES - SIDE EFFECTS AND LATE EFFECTS

## Cardiotoxicity

---

The anthracyclines, particularly doxorubicin (generic name Adriamycin), are known to cause heart failure in a subset of patients in a dose-dependent manner. In other words, the higher the cumulative dose, the larger number of patients who experience this effect. Anthracycline-induced cardiotoxicity appears to have two phases: an acute phase, in which symptoms develop during treatment, but are transient; and a late phase, in which cardiac damage progresses over time, eventually presenting as congestive heart failure as early as a year after treatment and up to a decade or more after treatment ([Brouwer, et al](#)). Late congestive heart failure can develop even in the absence of acute symptoms during treatment, and with the exception of broad guidelines (age, pre-existing cardiovascular conditions), there is no means of identifying at-risk patients. As described above, efforts to prevent cardiotoxicity through antioxidant or iron chelator pre-treatment have proven ineffective or, if effective against cardiotoxicity, also reduced anti-tumor action.

In the 1990s, when Herceptin began to be paired with Adriamycin in treating breast and other cancers, the incidence of cardiotoxicity increased sharply ([Slamon, 377a](#)). Cardiomyopathy (weakening of heart muscle or a change in heart muscle structure) is a known side effect of Herceptin alone, and its apparent compounding of anthracycline-induced cardiac damage has given researchers another angle for studying the cardiotoxicity of the anthracyclines.

## Liposomal Anthracyclines

---

Liposomal anthracyclines, or anthracyclines bound within a nano-scale liposome (artificial lipid capsules), represent the most significant strides today in reducing the cardiotoxicity of the drugs without compromising their effectiveness. Early clinical trials demonstrated significant decrease in the incidence of congestive heart failure, with comparable anti-cancer effectiveness ([Rivera](#)). The mechanism by which the lipid capsule helps reduce cardiotoxicity is not fully understood, but it is believed to be a product of the greater permeability of the microvasculature promoted by cancerous cells ([Rivera](#)). So, the lipid-encapsulated drug is simply taken up in greater quantities

by cancer cells because they produce "leakier" blood vessels. But the lipid capsule also slows the rate at which the drug binds to the proteins of healthy cells, and may deliver the chemotherapy over a longer period of time, potentially enhancing its effectiveness in comparison to standard formulations.

As a reminder that liposomal anthracyclines reduce, but do not eliminate, cardiotoxicity, all liposomal anthracyclines retain their US FDA "Black Box" warnings regarding cardiotoxicity and the need for close cardiac monitoring during treatment. And, clinical trial experience indicates that liposomal forms cause a higher incidence of painful and potentially debilitating hand-foot syndrome (Palmar-Plantar Erythrodysesthesia), in which the drug leaks from capillaries in the hands and feet and damages surrounding tissue.

Liposomal anthracyclines are sold under the following brand names:

- ♣ DaunoXome
- ♣ Doxil (Caelyx outside of the US)
- ♣ Myocet

### **Secondary Acute Myelogenous Leukemia (AML)**

---

Anthracyclines are also known to multiply the risk of developing acute myelogenous leukemia, a form of leukemia which is usually unresponsive to treatment and carries a poor prognosis.

Although the risk of developing AML increases several-fold after treatment with anthracyclines and certain other chemotherapies, the overall absolute risk remains low (estimated at less than 2% at ten years after treatment) ([Patt, et al, p. 560](#)).

Source : <http://www.toxipedia.org/display/toxipedia/Anthracyclines+-+Side+Effects+and+Late+Effects>