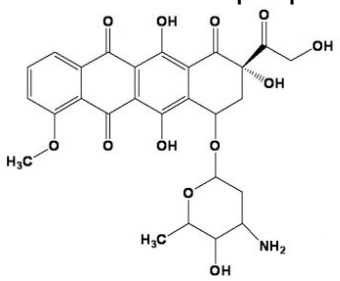
Doxorubicin (Adriamycin®):

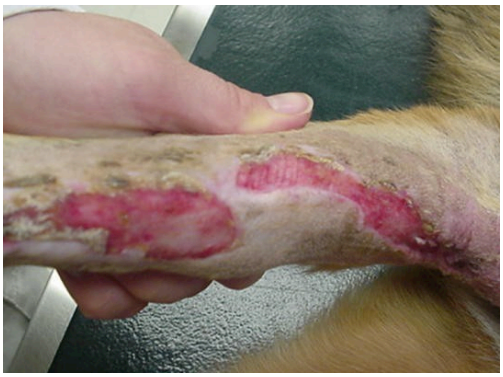
Doxorubicin is perhaps the most effective and commonly used broad-spectrum chemotherapy in veterinary oncology. This drug belongs to a family of drugs called **anthracyclines**. Other drugs within this class include *mitoxantrone* and*epirubicin*.

Anthracyclines are derived from the bacteria Streptomyces, and most also have antibiotic properties. This class of drug induces tumor cell death by



multiple mechanisms: 1) Doxorubicin inserts into the DNA of rapidly dividing cells, thereby inhibiting DNA synthesis; 2) Doxorubicin inhibits cellular enzymes such as topoisomerase I and II which are required from DNA replication and repair; 3) Doxorubicin also has the capacity to induce free radical/oxidative damage to cells ultimately leading to cell death. As discussed below, this later characteristic of free radical formation is likely the major mechanism responsible for one of the potential side effects of doxorubicin—cardiotoxicity.

Athracyclines are active in all phases of the cell cycle, and are therefore considered cell cycle non-specific chemotherapies (as apposed to antimicrotubule agents such as *vincristine* and *cytarabine* which are specific for certain phases of the cell cycle. Doxorubicin is very active against hematopoietic malignancies (i.e.*lymphoma*) is also commonly used against solid tumors, including*hemangiosarcoma* and *mammary carcinoma*.



Doxorubicin and other anthrcyclines are primarily eliminated via liver metabolism and therefore patients with liver disease should be dosed with caution. Additionally, these drugs are selectively eliminated from normal (and eventually tumor cells) via the MDR1 (multi-drug resistant gene-1) product P-glycoprotein. Animals lacking a functional P-glycoprotein (common in Collies and other herding breeds) are highly sensitive to this class of drugs, and should be dosed accordingly. A test is now available to determine whether a pet contains such a mutation in the MDR1 gene, and this test may be recommended prior to administration of doxorubicin in certain herding breeds.

Doxorubicin is administered IV every 2-3 weeks; side effects include those previously discussed (see Chemotherapy in Pets), including nausea, diarrhea, and bone marrow suppression, as well as potential damage to the heart muscle in dogs and renal tissue in cats. Doxorubicin cardiotoxicity can be either acute (reversible arrhythmias) or chronic (irreversible myocardial damage leading to DCM). This potential heart damage is primarily limited to large breed dogs and those predisposed to cardiac disease (Boxers, Doberman Pinschers, etc.).

In such breeds, or those with cardiac abnormalities noted on physical examination, we recommend performing a heart function exam (echocardiogram) before starting this drug. The risk of developing cardiotoxicity increases with the total number of doses administered and therefore, we often limit the total number of treatments to 5-6 total doses (150-180 mg/m2). By limiting the number of doses, less than 10% of all pets develop heart problems with this drug. Because of the potential renal side effects in cats, doxorubicin is generally not used in cats with underlying kidney disease.

An additional side effect of this drug is that it can cause severe tissue damage if administered outside of the vein. For this reason, a perfectly placed catheter is required for each treatment. If even a minute amount of drug is leaked around the catheter site, the end result may necessitate aggressive wound management and in extreme cases, amputation. For this reason, only highly trained and experienced staff are allowed to administer this drug.

Despite these potential side effects, doxorubicin is still considered relatively safe and well tolerated by most pets. It remains the mainstay for treatment of multiple tumor types including lymphoma and various solid tumors.