Doxorubicin: Insights into clinical applications

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Doxorubicin (Adriamycin), is an anthracycline antibiotic produced by the fungus Streptomyces peucetius⁴. Anthracyclines occupy a unique position among chemotherapy drugs, because this class of drugs has the most wide spectrum of activity against cancer².

Doxorubicin is one of the most commonly used chemotherapy drugs in cancer treatment, finding utility in variety of cancers³. The molecular structure of doxorubicin is composed of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine⁴.

Doxorubicin is mainly used in the following types of cancers.
- Breast cancer
- Hodgkin’s lymphoma
- Non-Hodgkin’s lymphoma
- Soft tissue sarcoma
- Ovarian cancer
- Lung cancer
- Bladder cancer
- Thyroid cancer
- Liver cancer
- Stomach cancer
- Wilm’s tumor
- Neuroblastoma
- Acute lymphoid leukemia

Description
Doxorubicin is a red colored powder that will appear as a red fluid when it is mixed and ready to be given. It is given only through the intravenous route. A central line like a port-a-cath is usually placed prior to administer doxorubicin.

Warnings
Administration: Doxorubicin is a very potent chemotherapy drug and should be used under close supervision of physician who is experienced in using chemotherapy drugs. Careful evaluation of the patient with labs and investigations including total blood count, chemistry panel with liver enzymes, and cardiac ejection should be done prior to initiating chemotherapy using doxorubicin. Patient should recover from side effects associated with prior administration of chemotherapy, prior to administering a new dose of doxorubicin to a patient. Patient should be followed very carefully after administration of doxorubicin since patients may develop very serious and life threatening complications from the treatment. Doxorubicin is a vesicant and special care should be taken to ensure the medication is not leaked out of the vein. Preferably this drug is administrated through a port-a-cath.

Cardiac Function: One of the major concerns while using doxorubicin is that the patient may develop cardiac dysfunction as a side effect from the treatment. Cardiac toxicity may appear as an acute or late event during the treatment. Early events are usually mild and self limiting. Acute toxicities usually take the form of cardiac arrhythmias and non-specific EKG changes including ST-T wave changes. Tachycardia and premature ventricular contractions may occur in the acute phase. Occasionally bradycardia associated with cardiac conduction defects may occur. Development of delayed cardiac toxicity is of much more concern than acute cardiac toxicities. Acute manifestations are rarely serious enough to halt the doxorubicin treatment. It is to be noted that development of acute cardiac toxicity is in no way predictive of future development of delayed cardiac toxicity.

Delayed cardiac toxicity is much more concerning from the view of side effects. This generally takes the form of cardiac muscle dysfunction leading to low left ventricular ejection fraction, with the development of congestive heart failure. This could be associated with shortness of breath, cardiomegalia, pleural effusion and hepatomegaly. In extreme cases life this may progress to life threatening cardiomyopathy. Development of delayed cardiac toxicity is intimately associated...
with the cumulative dose of doxorubicin used for treatment. If the cumulative dose is low (like 300 mg/m2) the probability for cardiac failure is low (about 1-2%), however with cumulative doses of 450 mg/m2, the risk increase to 5 to 8%. The risk goes as high as 20% with cumulative doses of 500 mg/m2. If patient has prior history of heart disease or history of radiation to area around heart, the risk is much higher and doxorubicin should be used with great caution in such patients\(^5\). Other factors like age of the patient and concurrent use of other cardiotoxic drugs should also be taken into account before deciding the maximum cumulative dose for a patient. Delayed cardiac toxicity of doxorubicin may occur several years after exposure to doxorubicin and patient who has received this drug should be monitored for several years after completing the chemotherapy. Treatment of doxorubicin induced congestive heart failure is not significantly different from treatment of congestive heart failure due to other causes. Drugs used in the treatment of doxorubicin related congestive heart failure include in digitalis, diuretics, and ACE inhibitors\(^6\).

**Secondary Leukemia:** Doxorubicin significantly increases the risk of secondary myelodysplastic syndrome (MDS) and acute leukemia. Risk of leukemia increases if patient is treated with a combination treatment as in AC which is the commonly used combination of doxorubicin and cyclophosphamide. Combination of doxorubicin and radiation therapy also increases the risk of leukemia. Prior history of treatment with other chemotherapy drugs also is shown to increases the risk of leukemia. Risk of developing MDS and acute leukemia is also related to cumulative doses of doxorubicin used in the treatment. Doxorubicin associated MDS and leukemia usually occur within 1-3 after exposure to the drug. It is estimated that 5 year risk of developing leukemia from doxorubicin treatment is about 1 in 200\(^7\).

**Pregnancy:** Doxorubicin is a pregnancy category D drug and this drug is teratogenic and toxic to the embryo at a fraction of doses that are usually used for clinical practice. Animal studies have shown that most characteristic malformations were fistulas, hypoplasias and atresias involving esophagus and intestine. Women should be strongly cautioned against pregnancy while they are undergoing treatment using doxorubicin. If a patient becomes pregnant during treatment, the patient should be counseled regarding the possibility of health hazards and malformation to the fetus\(^8,9\).

**Use in elderly:** There is abundant clinical trial experience to say that elderly patients (as defined by age 65 and older) usually tolerate doxorubicin at standard doses. Also clinical efficiency of doxorubicin remains unabated in the elderly population. It should not be forgotten that elderly patients often have multiple co-morbid illness and it goes without saying that these patients are at a higher risk of developing complications from doxorubicin. Doxorubicin should be used with caution in elderly patients and the decision to use doxorubicin should be taken after careful analysis of risks and benefits involved in the treatment\(^10\).

**Administration:** Doxorubicin should be administered with extreme care. Special care should be taken to ensure that the drug does not extravasate. Extravasation usually causes a burning sensation, but extravasation also could occur without the warning of this burning sensation. Doxorubicin is best administered through a central venous access like a port-a-cath or PICC line. Extravasation can be extremely dangerous since the contact of the drug with muscles and tissues can cause significant damage, which may cause blistering, ulceration and disfigurement often needing plastic surgical interventions. If there is any suspicion that extravasation has occurred, the infusion should be stopped immediately. If extravasation has occurred, intermittent application of ice to the site has to be applied for 15 to 20 minutes. There are reports of various local applications being beneficial, but the value of these remedies remains unproven. Patient should be closely followed for the extent of damage to the tissue and a plastic surgery consult may be indicated.

**Dosage:** Doxorubicin is used in various doses depending upon the regimen and concurrent use of other chemotherapeutic agents in combination. Most commonly used dosage for doxorubicin is 60 to 75 mg/m2 given in cycles of 21 days. Patients with poor cardiac function, co-morbid
illnesses, and poor bone marrow reserve should receive lower doses. When used in combination with other drugs typical doses range from 40 to 60 mg/m2 given once in 3 weeks to 4 weeks cycles. One of the most commonly used regimen involving doxorubicin is named AC, which is an acronym for combination of doxorubicin and cyclophosphamide used in adjuvant treatment of breast cancer as well as in metastatic breast cancer. In this regimen doxorubicin is used in dosage of 60mg/m2 with cyclophosphamide 600 mg/m2 given once every 21 days.

**Mechanism of action**
Doxorubicin has ability to inhibit cell division and cause cell death. Doxorubicin forms complexes with DNA by intercalation between base pairs causing inhibition of topoisomerase II which relaxes supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication\(^\text{11, 12, 13}\).

**Metabolism and excretion:** Initial break down of doxorubicin takes place in liver with the production of aglycones\(^\text{14, 15}\). This is followed by formation of free radicals and these free radicals are thought to be the causative agents of cardiotoxicity\(^\text{16}\). About 40% of the given dose appears in bile within 5 days. Only 5 to 10% of the drug is excreted through urine. Clearance of the drug is delayed in overweight women\(^\text{17}\).

**Side effects**
Side effects associated with doxorubicin chemotherapy may vary from person to person. Some patients may experience significant side effects while others may experience very minimal side effects. It is not possible to predict who is going to have more severe side effects. Most patients will have the common side effects like hair loss, while some other side effects like cardiotoxicity may affect some patients, but not others.

**Cardiac toxicity:** Cardiac toxicity is mentioned in detail in the warning section above. Patient who is undergoing treatment using doxorubicin should undergo regular cardiac evaluation to determine the left ventricular ejection fraction. Patient needs a baseline measurement of Ejection fraction and this should be repeated during the course of the chemotherapy if there is a concern for developing cardiac toxicity. If patient is receiving higher cumulative doses of doxorubicin, repeat cardiac evaluation should be done routinely. Patients with cardiac diseases and those who are high risk for developing left ventricular dysfunction (like people with history of mediastinal radiation and those who are on concurrent cardiotoxic medications) should undergo close monitoring with repeat evaluation of left ventricular ejection fraction while on treatment\(^\text{18, 19}\).

If there is strong suspicion of cardiac toxicity from doxorubicin, patient may undergo a cardiac muscle biopsy. This is a very sensitive test to detect doxorubicin induced cardiomyopathy\(^\text{20}\). In most patients cardiac biopsy is not required and diagnosis is made on clinical grounds with non-invasive tests like EKG and echo cardiogram. EKG may show dysrhythmias or a reduced voltage QRS complex. If patient is noted to have a 20% decline in left ventricular ejection fraction during treatment, this might indicate worsening in cardiac function and the patient should be monitored for development of congestive heart failure. In doubtful situations the benefit of continuing with doxorubicin should be carefully balanced with the risk of irreversible congestive heart failure and life threatening cardiac arrhythmias.

**Bone marrow suppression:** Use of doxorubicin like many other chemotherapy drugs can cause myelosuppression resulting in anemia, thrombocytopenia and leucopenia. Neutropenia may result in significant impairment of immune function exposing the patient to risks of serious and life threatening infections. Patient should be carefully monitored with complete blood counts and differential after each cycle of chemotherapy. If clinically indicated patient should be given prophylactic white cell growth factors like filgrastim or peg-filgrastim. Blood counts usually fall in one week and reach a nadir by 10\(^\text{th}\) day and then recover by about day 14. Chemotherapy using doxorubicin is usually given once every 21
Impairment of Fertility: Animal models have suggested that doxorubicin causes impairment of fertility in mouse with 1/50 dose equivalent of human based on body surface area. A single injection of 1/100 of recommended human dose on a body surface area basis is shown to induce testicular atrophy and oligospermia in rats. Doxorubicin has shown to induce mutations in animals and this could very well be true in human beings as well. Combination chemotherapy using doxorubicin and other chemotherapeutic agents has shown to cause oligospermia or azoospermia in men\(^{23}\). Since doxorubicin can potentially cause chromosomal changes in sperms, men receiving this drug should use contraceptive methods to prevent pregnancy. Doxorubicin may cause temporary amenorrhea during the course of treatment, however in younger patients the menstrual cycle may return with preservation of fertility. In older menstruating women doxorubicin may cause premature menopause.

Contraception and breast feeding: Many patients who receive doxorubicin are women in reproductive age group. It is critical that the patient would not become pregnant while receiving doxorubicin-containing chemotherapy. Patient should be warned against risk of pregnancy and should be instructed to use effective contraceptive methods to prevent any chance of pregnancy while receiving doxorubicin-containing chemotherapy. Doxorubicin can cause damage to the developing fetus. Doxorubicin may be excreted in breast milk and nursing mothers should be advised, not to breast feed their babies\(^{24}\).

Alopecia: Alopecia is very common side effect of doxorubicin chemotherapy. Most of the patients who receive doxorubicin chemotherapy will have alopecia. This usually starts 3-4 weeks after the first dose of doxorubicin, and may gradually worsen with subsequent doses of doxorubicin containing chemotherapy. Alopecia may sometime be very severe and may result in total hair loss. Hair may also be lost from other areas of the body including eyebrows and eyelashes. In most cases the alopecia is reversible and will grow back once the chemotherapy is completed\(^{25}\).

Skin and nail changes: Doxorubicin may cause hyperpigmentation of the palm and other areas of the skin. Nail changes including onycholysis may occur\(^{26}\). White lines or ridges may appear on the nails. The nails usually grow out of these changes once the treatment is completed. In patients who have received radiation a phenomenon known as “radiation recall” or “radiation recall dermatitis” may occur. This refers to an acute inflammatory reaction that occurs in previously irradiated areas of the skin. The exact mechanism of this skin reaction is not well understood. There are several chemotherapy drugs that may cause “radiation recall dermatitis” and this includes doxorubicin, docetaxel, paclitaxel, gemcitabine and capecitabine. “Radiation recall” risk decrease with passage of time from radiation\(^{27}\).

Nausea and vomiting: Patient may experience severe nausea and vomiting during and after

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administration of the chemotherapy. Nausea and vomiting are usually controlled by 5-HT3 antagonists like ondansetron\textsuperscript{28}.

**Diarrhea:** Severe Diarrhea may occur during chemotherapy treatment with doxorubicin. This is usually mild and can usually be easily controlled with medications. Patient should be advised to drink plenty of water to correct dehydration. If the diarrhea becomes severe patient may require treatment in the hospital with intravenous hydration.

**Mucositis:** Inflammation and ulceration of the mouth and esophagus may occur after administration of doxorubicin. This may occurs during the second or third week after administration of the drug. Mucositis may lead to ulceration and this may serve as a focus of infection bacterial especially when the patient is neutropenic. Occasionally these lesions get further complicated with the growth of superinfection by candida albicans. Ulceration may not be limited to mouth or esophagus and in fact can affect the entire gastrointestinal system. Ulceration may sometimes progress to necrosis of the colon and may lead to sepsis especially in a neutropenic patient. Patient may also experience lack of appetite, abdominal pain, and diarrhea.

**Hypersensitivity:** Doxorubicin may occasionally cause hypersensitivity reactions including skin rash, urticaria and overt anaphylactic reactions.

**Neurological:** Treatment using doxorubicin may cause peripheral neuropathy and this may manifest in the form of sensory or motor disturbances. Peripheral neuropathy is most commonly reported when this drug is used in combination with other drugs like Cisplatin or cyclophosphamide\textsuperscript{29}. Combination of doxorubicin and Cisplatin may cause other neurological side effects including seizure and coma.

**Red colored urine:** Treatment using doxorubicin may cause the color of urine to turn red. Some patients gets nervous about passing red colored urine and it is imperative that patients be warned that this could happen. This effect may last for about 24 hours after the treatment. Apart from patient’s anxiety there are no adverse effects involved with this urine discoloration.

**Sensitivity to sunlight:** Doxorubicin may make the skin the skin over-sensitive to sunlight. Sunburn may occur with excess sun exposure. This effect may last for several months even after completion of the treatment. Patients should be warned to apply a high protection factor sun cream and protective clothing when going out in the sun.

**Tiredness and a general feeling of weakness:** This probably is the most commonly reported side effect of treatment using doxorubicin. In many cases, doxorubicin is used in combination with other chemotherapy drugs and the feeling of fatigue, tiredness and lack of energy mostly related to combination chemotherapy rather than due to doxorubicin.

**Contraindications**

If patient’s absolute neutrophil count is less than 1500, doxorubicin should be avoided to prevent significant drop in the counts which may lead to neutropenic fever. Patients with severe liver impairment should not receive doxorubicin. Doxorubicin is also contraindicated in patients with recent myocardial infarction, congestive heart failure, and severe cardiac dysarrhythmias.

**Drug-drug interactions**

Liver is the major organ in metabolizing doxorubicin. Any drug that may share the metabolism through liver may potentially interact with doxorubicin. Toxicities and side effects associated with doxorubicin are enhanced when this drug is used in combination with other chemotherapeutic drugs that share similar side effects.

**Paclitaxel:** Several studies have suggested that co-administration of doxorubicin and paclitaxel may significantly increase cardiac toxicity of doxorubicin. If these two drugs are to be given together, it is suggested that paclitaxel be infused over 24 hours followed by doxorubicin administration over 48 hours to minimize cardiac toxicity\textsuperscript{30}.

**Progesterone:** Administration of progesterone with doxorubicin may cause increased incidence of neutropenia and thrombocytopenia.
**Cyclosporine:** Concurrent use of cyclosporine and doxorubicin may result in decreased metabolism and elimination of doxorubicin resulting in increased levels of the drug with increased toxicity from doxorubicin. This may result in profound and prolonged cytopenia.

**Verapamil:** Concurrent use of verapamil and doxorubicin may lead to increased peak concentration of doxorubicin in the heart and this may lead to greater cardiac toxicity.

**Dexrazoxane:** Dexrazoxane has the ability to mitigate cardiotoxic effects of doxorubicin. A combination of dexrazoxane and doxorubicin is sometimes used in clinical practice, when the cumulative dose of doxorubicin has exceeded 300 mg/m² and patient is still responding to treatment. In this situation it has been demonstrated that addition of dexrazoxane is not associated with decrease clinical activity of doxorubicin. In other situations combination of dexrazoxane and doxorubicin is to be avoided because this may affect the outcome of the treatment.

**Cytarabine:** A combination of doxorubicin and cytarabine is to be avoided since this may lead to severe infections including necrotizing colitis.

**Cyclophosphamide:** Doxorubicin is often combined with cyclophosphamide; however the combination may increase toxicity of doxorubicin and increases risk of developing leukemia. Doxorubicin has shown to increase the risk of hemorrhagic cystitis that is associated with cyclophosphamide treatment.

**Other drug-drug interactions:** Data suggest that various sources suggests that doxorubicin may interact with the following drugs as well. Phenobarbital (lowers efficiency of doxorubicin). Phenytoin (doxorubicin reduced phenytoin levels); streptozocin (increase toxicity from doxorubicin) saquinavir (increases mucositis from doxorubicin)

**Overdose**
Overdose of doxorubicin causes more severe side effects including severe neutropenia, anemia, thrombocytopenia and mucositis. In an overdosed patient prophylactic doses of filgrastim or peg-filgrastim may be decrease the intensity of cytopenia. Patient may require transfusion support if hematocrit or platelet count falls to critical values. Pain and discomfort due to mucositis may be ameliorated by use of any of the local anesthesia containing preparations³¹.
References


2. Weiss RB. "The anthracyclines: will we ever find a better doxorubicin?". Seminars in Oncology 19 (6): 670–86.


