= Doxorubicin =

Doxorubicin , sold under the trade names Adriamycin among others , is a medication used in cancer chemotherapy . It is derived by chemical semisynthesis from a bacterial species . It is an anthracycline antitumor antibiotic (note : in this context , this does not mean it is used to treat bacterial infections) closely related to the natural product daunomycin and like all anthracyclines , it works by intercalating DNA , with the most serious adverse effect being life @-@ threatening heart damage . It is commonly used in the treatment of a wide range of cancers , including hematological malignancies (blood cancers , like leukaemia and lymphoma) , many types of carcinoma (solid tumours) and soft tissue sarcomas . It is often used in combination chemotherapy as a component of various chemotherapy regimens .

Common adverse effects of doxorubicin include hair loss (seen in most of those treated with the drug) , myelosuppression (a compromised ability of the body 's bone marrow to produce new blood cells) , nausea and vomiting (which are seen in roughly 30 @-@ 90 % of people treated with the drug) , oral mucositis , oesophagitis , diarrhoea , skin reactions (including hand @-@ foot syndrome) and localised swelling and redness along the vein in which the drug is delivered . Less common , yet serious reactions include hypersensitivity reactions (including anaphylaxis) , radiation recall , heart damage and liver dysfunction . Some people experience red discoloration of their urine , sometimes for up to 1 to 2 days after treatment .

Doxorubicin is on the World Health Organization 's List of Essential Medicines , the most important medication needed in a basic health system . The drug is administered intravenously as a hydrochloride salt . Doxorubicin is photosensitive , and containers are often covered by an aluminum bag and / or brown wax paper to prevent light from affecting it . Doxorubicin is also available in liposome @-@ encapsulated forms as Doxil (pegylated form) , Myocet (nonpegylated form) , and Caelyx , although these forms must also be given by intravenous injection .

= = Medical use = =

Doxorubicin is commonly used to treat some leukemias and Hodgkin 's lymphoma , as well as cancers of the bladder , breast , stomach , lung , ovaries , thyroid , soft tissue sarcoma , multiple myeloma , and others . Commonly used doxorubicin @-@ containing regimens are AC (Adriamycin , cyclophosphamide) , TAC (Taxotere , AC) , ABVD (Adriamycin , bleomycin , vinblastine , dacarbazine) , BEACOPP , CHOP (cyclophosphamide , hydroxydaunorubicin , vincristine , prednisone) and FAC (5 @-@ fluorouracil , adriamycin , cyclophosphamide) .

Doxil (see below) is used primarily for the treatment of ovarian cancer where the disease has progressed or recurred after platinum @-@ based chemotherapy , or for the treatment of AIDS @-@ related Kaposi 's sarcoma .

= = = Liposomal formulations = = =

There is a pegylated (polyethylene glycol coated) liposome @-@ encapsulated form of doxorubicin , sold as Doxil . It was developed to treat Kaposi 's sarcoma , an AIDS @-@ related cancer that causes lesions to grow under the skin , in the lining of the mouth , nose and throat , or in other organs . The polyethylene glycol coating results in preferential concentration of doxorubicin in the skin . However , this also results in a side effect called palmar plantar erythrodysesthesia (PPE) , more commonly known as hand @-@ foot syndrome . Following administration of this form of doxorubicin , small amounts of the drug can leak from capillaries in the palms of the hands and soles of the feet . The result of this leakage is redness , tenderness , and peeling of the skin that can be uncomfortable and even painful . In clinical testing at 50 mg / m2 dosing every 4 weeks , half of people developed hand @-@ foot syndrome . The rate of this side effect limits the dose of this formulation that can be given as compared with plain doxorubicin in the same treatment regimen , thereby limiting potential substitution . Substitution would be desirable because liposome @-@ encapsulated doxorubicin is less cardiotoxic than unencapsulated doxorubicin . This form is also

approved by the FDA for treatment of ovarian cancer and multiple myeloma .

A non @-@ pegylated liposomal doxorubicin , called Myocet , is approved in Europe and Canada for treatment of metastatic breast cancer in combination with cyclophosphamide , but has not been approved by the FDA for use in the United States . Unlike Doxil , the Myocet liposome does not have a polyethylene glycol coating , and therefore does not result in the same rate of hand @-@ foot syndrome . The minimization of this side effect may allow for one for one substitution with doxorubicin in the same treatment regimen , thereby improving safety with no loss of efficacy . Like Doxil , the liposomal encapsulation of the doxorubicin limits the cardiotoxicity . In theory , by limiting the cardiotoxicity of doxorubicin through liposomal encapsulation , it can be used safely in concurrent combination with other cardiotoxic chemotherapy drugs , such as trastuzumab . There is an FDA black box warning that trastuzumab cannot be used in concurrent combination with doxorubicin , only in sequential combination . Though concurrent combination of trastuzumab and doxorubicin in clinical studies found superior tumor response , the combination resulted in unacceptable cardiotoxicity , including risk of cardiac failure manifesting as congestive heart failure (CHF) . Published phase II study results have shown that Myocet , trastuzumab , and paclitaxel can safely be used concurrently without the cardiac risk , as measured by reduction in LVEF function , while still achieving superior tumor response . This finding is the basis for the ongoing phase III trial for FDA approval .

= = Adverse effects = =

The most dangerous side effect of doxorubicin is cardiomyopathy , leading to congestive heart failure . The rate of cardiomyopathy is dependent on its cumulative dose , with an incidence about 4 % when the dose of doxorubicin is 500 ? 550 mg / m ² , 18 % when the dose is 551 ? 600 mg / m ² and 36 % when the dose exceeds 600 mg / m ² . There are several ways in which doxorubicin is believed to cause cardiomyopathy , including oxidative stress , downregulation of genes for contractile proteins , and p53 mediated apoptosis . The drug dexrazoxane is used to mitigate doxorubicin 's cardiotoxicity .

Another common and potentially fatal complication of doxorubicin is typhlitis , an acute life @-@ threatening infection of the bowel .

Additionally , some patients may develop PPE , characterized by skin eruptions on the palms of the hand or soles of the feet , swelling , pain , and erythema .

Due to these side effects and its red color , doxorubicin has earned the nickname " red devil " or " red death . "

Chemotherapy can cause reactivation of hepatitis B , and doxorubicin @-@ containing regimens are no exception .

Doxorubicin and several chemotherapeutic drugs (including cyclophosphamide) cause dyspigmentation . Other groups of drugs that cause this problem include antimalarials , amiodarone , heavy metals (but not iron) , tetracyclines , and antipsychotics .

= = Biosynthesis = =

Doxorubicin (DXR) is a 14 @-@ hydroxylated version of daunorubicin , the immediate precursor of DXR in its biosynthetic pathway . Daunorubicin is more abundantly found as a natural product because it is produced by a number of different wild type strains of Streptomyces . In contrast , only one known non @-@ wild type species , Streptomyces peucetius subspecies cesius ATCC 27952 , was initially found to be capable of producing the more widely used doxorubicin . This strain was created by Arcamone et al. in 1969 by mutating a strain producing daunorubicin , but not DXR , at least in detectable quantities . Subsequently , Hutchinson 's group showed that under special environmental conditions , or by the introduction of genetic modifications , other strains of Streptomyces can produce doxorubicin . His group has also cloned many of the genes required for DXR production , although not all of them have been fully characterized . In 1996 , Strohl 's group discovered , isolated and characterized dox A , the gene encoding the enzyme that converts

daunorubicin into DXR . By 1999 , they produced recombinant dox A , a cytochrome P450 oxidase , and found that it catalyzes multiple steps in DXR biosynthesis , including steps leading to daunorubicin . This was significant because it became clear that all daunorubicin @-@ producing strains have the necessary genes to produce DXR , the much more therapeutically important of the two . Hutchinson 's group went on to develop methods to improve the yield of DXR , from the fermentation process used in its commercial production , not only by introducing dox A encoding plasmids , but also by introducing mutations to deactivate enzymes that shunt DXR precursors to less useful products , for example baumycin @-@ like glycosides . Some triple mutants , that also over @-@ expressed dox A , were able to double the yield of DXR . This is of more than academic interest , because at that time DXR cost about $ 1 @.@ 37 million per kg and current production in 1999 was 225 kg per annum . More efficient production techniques have brought the price down to $ 1 @.@ 1 million per kg for the nonliposomal formulation . Although DXR can be produced semi @-@ synthetically from daunorubicin , the process involves electrophilic bromination and multiple steps , and the yield is poor . Since daunorubicin is produced by fermentation , it would be ideal if the bacteria could complete DXR synthesis more effectively .

= = Mechanism of action = =

Doxorubicin interacts with DNA by intercalation and inhibition of macromolecular biosynthesis . This inhibits the progression of the enzyme 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 . It may also increase quinone type free radical production , hence contributing to its cytotoxicity .

The planar aromatic chromophore portion of the molecule intercalates between two base pairs of the DNA , while the six @-@ membered daunosamine sugar sits in the minor groove and interacts with flanking base pairs immediately adjacent to the intercalation site , as evidenced by several crystal structures .

By intercalation , doxorubicin can also induce histone eviction from transcriptionally active chromatin . As a result , DNA damage response , epigenome and transcriptome are deregulated in doxorubicin @-@ exposed cells .

= = History = =

In the 1950s , an Italian research company , Farmitalia Research Laboratories , began an organized effort to find anticancer compounds from soil @-@ based microbes . A soil sample was isolated from the area surrounding the Castel del Monte , a 13th @-@ century castle . A new strain of Streptomyces peucetius , which produced a red pigment , was isolated , and an antibiotic from this bacterium was effective against tumors in mice . Since a group of French researchers discovered the same compound at about the same time , the two teams named the compound daunorubicin , combining the name Dauni , a pre @-@ Roman tribe that occupied the area of Italy where the compound was isolated , with the French word for ruby , rubis , describing the color . Clinical trials began in the 1960s , and the drug was successful in treating acute leukemia and lymphoma . However , by 1967 , it was recognized that daunorubicin could produce fatal cardiac toxicity .

Researchers at Farmitalia soon discovered that changes in biological activity could be made by minor changes in the structure of the compound . A strain of Streptomyces was mutated using N @-@ nitroso @-@ N @-@ methyl urethane , and this new strain produced a different , red @-@ colored antibiotic . They named this new compound Adriamycin , after the Adriatic Sea , and the name was later changed to doxorubicin to conform to the established naming convention . Doxorubicin showed better activity than daunorubicin against mouse tumors , and especially solid tumors . It also showed a higher therapeutic index , yet the cardiotoxicity remained .

Doxorubicin and daunorubicin together can be thought of as prototype compounds for the

anthracyclines . Subsequent research has led to many other anthracycline antibiotics , or analogs , and there are now over 2 @,@ 000 known analogs of doxorubicin . By 1991 , 553 of them had been evaluated in the screening program at the National Cancer Institute (NCI) . In 2016 GPX @-@ 150 was granted Orphan Drug designation by US FDA .

= = Society and culture = =

= = = Names = = =

It is also known as hydroxydaunorubicin and hydroxydaunomycin .
It is sold under a number of different brand names , including Adriamycin PFS , Adriamycin RDF , or Rubex .

= = = Shortage = = =

As of February 2014 , Doxil was available in limited supply . In 2011 , Doxil became available only in very limited supply due to production problems with the third @-@ party manufacturer . Johnson & Johnson (JNJ) , through its subsidiary Janssen Products , LP , had been receiving its Doxil supply from contract manufacturer Ben Venue Laboratories (located in Bedford , Ohio) , a unit of Boehringer Ingelheim GmbH of Germany . The problems began when Ben Venue temporarily shut down their manufacturing facility due to quality control issues .
In February 2012 , to address the Doxil shortage , the US Food and Drug Administration (FDA) allowed for the temporary importation of Lipodox , which contains the same active ingredient as Doxil and is made by Sun Pharma Global FZE (Sun) , a subsidiary of India 's Sun Pharmaceutical Industries Ltd . The agency said it intends to continue allowing the importation of Lipodox until Sun has made enough generic Doxil to meet demand .
The FDA approved the first generic version of Doxil , made by Sun , in February 2013 . It will be available in 20 milligram and 50 milligram vials .

= = Research = =

Combination therapy experiments with sirolimus (rapamycin) and doxorubicin have shown promise in treating Akt @-@ positive lymphomas in mice .
Recent animal research coupling a murine monoclonal antibody with doxorubicin has created an immunoconjugate that was able to eliminate HIV @-@ 1 infection in mice . Current treatment with antiretroviral therapy (ART) still leaves pockets of HIV within the host . The immunoconjugate could potentially provide a complementary treatment to ART to eradicate antigen @-@ expressing T cells .

= = = Antimalarial activity = = =

There is some evidence for antimalarial activity for doxorubicin and similar compounds . In 2009 , a compound similar in structure to doxorubicin was found to inhibit plasmepsin II , an enzyme unique to the malarial parasite Plasmodium falciparum . The pharmaceutical company GlaxoSmithKline (GSK) later identified doxorubicin in a set of compounds that inhibit parasite growth