Doxorubicin

Drug type
- An anthracycline antibiotic that has antineoplastic activity
- Also available in a liposomal version
- The dose of liposomal doxorubicin is different from that of conventional doxorubicin, and the two formulations are not interchangeable
- Liposomal delivery improves drug penetration into tumors and decreases drug clearance, thereby increasing the duration of therapeutic drug effects

Indications
- Used to treat acute lymphoblastic leukemia, acute myeloblastic leukemia, breast cancer, bronchogenic lung cancer, gastric cancer, Kaposi sarcoma related to AIDS, malignant lymphoma (Hodgkin and non-Hodgkin), neuroblastoma, ovarian cancer, soft tissue and osteogenic sarcomas, thyroid cancer, transitional cell bladder cancer, Wilms tumor
- Also used to treat Ewing tumor; squamous cell carcinoma of the head, neck, cervix, and vagina; carcinoma of the testes, prostate, and uterus; and refractory multiple myeloma

Mechanism of action
- Intercalates between base pairs in the DNA helix, thereby preventing DNA replication and ultimately inhibiting protein synthesis
- Inhibits topoisomerase II, which results in an increased and stabilized cleavable enzyme-DNA linked complex during DNA replication and subsequently prevents the ligation of the nucleotide strand after double-strand breakage
- Forms oxygen free radicals resulting in cytotoxicity secondary to lipid peroxidation of cell membrane lipids; the formation of oxygen free radicals also contributes to drug toxicity, namely the cardiac and cutaneous vascular effects

How to administer
- IV adminstration only (potent vesicant)
  - If extravasation occurs, it may lead to severe local tissue damage resulting in ulceration, necrosis, and pain

Dosage and administration
- Children
  - 35-75 mg/m^2 q21d, or 20-30 mg/m^2/wk, or 60-90 mg/m^2 continuous IV infusion over 96 hours q3-4wk
- Adults
  - 60-75 mg/m^2 IV injection q21d, or 60 mg/m^2 q2wk, or 40-60 mg/m^2 q3-4wk
  - 20-30 mg/m^2 for 2-3 days q4wk
  - 20 mg/m^2 once a week
  - Dose adjustments are based on hepatic impairment and the severity of neutropenic fever/infection

Pregnancy category: D

Lactation
- Enters into breast milk
- Breast-feeding while taking doxorubicin is not recommended

Black box warning
- May cause cumulative, dose-related myocardial toxicity (early or delayed)
- Probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction is estimated to be

  - 1% to 2% at a total cumulative dose of 300 mg/m^2
  - 3% to 5% at a dose of 400 mg/m^2
  - 5% to 8% at a dose of 450 mg/m^2
  - 6% to 20% at a dose of 500 mg/m^2
- Risk of developing heart failure (HF) increases rapidly with increasing total cumulative doses of more than 450 mg/m^2

Cautions and adverse effects

- Pediatric: Risk of delayed cardiotoxicity and HF, prepubertal growth failure
- Geriatric: Cardiotoxicity more frequent, bone marrow reserves may be inadequate
- Most frequently reported adverse reactions: alopecia, esophagitis, infection, leukopenia, nausea, stomatitis, urine or tear discoloration, vomiting
- Less frequent: chronic HF, diarrhea, GI ulcer, hyperuricemia, injection site sequelae, nail discoloration, phlebosclerosis, postirradiation erythema, skin thickening, thrombocytopenic disorder, tissue necrosis, uric acid nephropathy, gout
- Rare: allergic dermatitis, allergic reactions, anaphylaxis, bronchospastic pulmonary disease, cardiotoxicity, drug fever, dyspnea, extravasation injury, myelodysplastic syndrome, pruritus of skin, severe bone marrow depression, skin rash, urticaria, wheezing

Drug interactions

- Clearly contraindicated drug combinations
  - Immunosuppressives, immunomodulators/efalizumab (Raptiva), natalizumab (Tysabri), live vaccines
- Severe interaction
  - Doxorubicin may increase the concentrations of 2B6 substrates, leflunomide (Arava, generics), vitamin K antagonists
  - Levels of doxorubicin may be increased by bevacizumab (Avastin), cyclosporine (Neoral, Sandimmune, Gengraf, generics), darunavir (Prezista), dasatinib (Sprycel), sorafenib (Nexavar)
- Herbals:
  - Avoid St. John's Wort, echinacea, black cohosh, and dong quai
- Severe interaction
  - Selected chemotherapy agents: bevacizumab, dasatinib, trastuzumab (Herceptin), taxanes, sorafenib
  - Stavudine (Zerit, generics), zidovudine (Retrovir, generics), warfarin (Coumadin, Jantoven, generics)
- Moderate interaction
  - Digoxin (Digitek, Lanoxicaps, Lanoxin, generics)

What to tell your patient

- Doxorubicin is a chemotherapy drug that works by slowing or stopping the growth of cancer cells
- Your doctor has prescribed this medication because he or she has judged that the benefit is greater than the risk of side effects
- Many patients on doxorubicin do not have serious side effects
- Contact your health care provider immediately if you should experience any of the following symptoms:
  - Fever of 100.5°F (38°C), chills (possible infection)
  - Blistering, pain, burning sensation, or swelling at the IV site
  - Shortness of breath, wheezing, difficulty breathing, closing up of the throat, swelling of facial features, hives (possible allergic reactions)
- Contact your health care provider within 24 hours of noticing any of the following:
  - Mouth sores (painful redness, swelling, or ulcers)
  - Nausea (interferes with ability to eat and unrelieved with prescribed medication)
  - Vomiting (vomiting more than 4 to 5 times in a 24-hour period)
  - Diarrhea (4 to 6 episodes in a 24-hour period)
  - Fast or irregular heartbeats
  - Unusual bleeding or bruising
  - Black or tarry stools or blood in your stools or urine
  - Extreme fatigue (bad enough that you cannot carry on self-care activities)
  - Swelling of the feet or ankles ■

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