Liposomal Doxorubicin

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Drug name: Doxorubicin hydrochloride liposome injection is commonly known as Doxil® (Alza Pharmaceuticals, Mountain View, CA) and liposomal doxorubicin.

Classification: Liposomal doxorubicin is a cytotoxic anthracycline antibiotic.

Action: Liposomal doxorubicin binds with DNA and inhibits nucleic acid synthesis. The uniqueness of this form of doxorubicin is that it is encapsulated in long-acting STEALTH® liposomes composed of phospholipid that help to protect the drug from detection by the mononuclear phagocyte system. This allows the drug to circulate longer in the system and penetrate the altered, and often compromised, vasculature of tumors. Liposomal encapsulation can affect a drug's functional properties relative to those of the unencapsulated form; *therefore, liposomal doxorubicin should not be substituted for doxorubicin HCl* (Adriamycin RDF/PFS®, Pharmacia & Upjohn, Peapack, NJ; Rubex®, Bristol-Myers Squibb Oncology/Immunology, Princeton, NJ).

Indications: Liposomal doxorubicin is indicated for the treatment of metastatic ovarian cancer that is refractory to both paclitaxel and platinum-based chemotherapy. The drug also is used to treat HIV-associated Kaposi's sarcoma that has progressed after prior combination chemotherapy or in patients who are intolerant to therapy. Liposomal doxorubicin is being investigated as first-line treatment for locally advanced breast cancer and metastatic breast cancer and as a treatment for other gynecologic malignancies and previously untreated advanced sarcomas.

Metabolism: Liposomal doxorubicin metabolism is not fully understood; metabolism of the drug may occur in the liver, plasma, or both.

Excretion: Renal

Half-life: 45–55 hours

Effect on blood counts: The effect of liposomal doxorubicin on patients' blood counts depends on the disease being treated. Leukopenia was observed in 60%, anemia occurred in 20%, and thrombocytopenia occurred in 20% of the patients with Kaposi's sarcoma who received the drug. Among patients with ovarian cancer, anemia is the most common hematologic effect (52.6%), followed by leukopenia (42.2%) and thrombocytopenia (24.2%). For all patients who receive the drug, myelosuppression is a major dose-limiting side effect and may require dose modification. The absolute neutrophil count must be greater than 1,500/mm^3, and the platelet count must be greater than 75,000/mm^3 for treatment. Hematologic growth factors may be needed for patients receiving liposomal doxorubicin.

Adverse reactions and effects: Liposomal doxorubicin administration may cause flushing, headache, facial swelling, shortness of breath, chills, back and chest pain, throat tightness, and hypotension. These infusion-related reactions have been observed in 5%–10% of patients, and in most patients, these reactions have resolved over the course of several hours. If a reaction occurs, the infusion should be stopped, the physician should be notified, and medications should be administered as directed (usually diphenhydramine and hydrocortisone). The infusion may be restarted at a slower rate. Patients at risk for an infusion-related reaction include those with asthma and a history of drug allergies and reactions. In clinical studies, patients who were at risk or had a previous reaction were premedicated with diphenhydramine, hydrocortisone, and a histamine H2 antagonist. Reactions appear to be rate-related and are most likely caused by the liposome component of liposomal doxorubicin.

Stomatitis is a dose-limiting side effect, seen more frequently with higher doses (e.g., doses used in the treatment of ovarian cancer). The development of mouth ulcerations may require dose delays of up to two weeks and possible dose reductions.

Another dose-limiting side effect that was observed in 37.4% of patients (with 16.4% being dose-limiting) is palmar-plantar erythrodysesthesia (PPE), commonly known as "hand and foot syndrome." Early symptoms include tingling, burning, redness, swelling, and small blisters or sores of the hands and feet. PPE also may affect areas of friction and pressure, such as the groin and area behind the knees. Symptoms may progress to skin sloughing and desquamation. PPE usually occurs with the second or third cycle of treatment, and dose delays of up to two weeks may be needed. If symptoms persist, the drug may need to be discontinued.

Experience with liposomal doxorubicin-induced cardiac toxicity is limited. Researchers believe that the cardiotoxicity potential of this drug is similar to that of conventional (unencapsulated) doxorubicin. Prior use of anthracycline therapy, radiation to the mediastinal area, or concomitant therapy with a cardiotoxic agent, such as cyclophosphamide, may increase the risk of cardiotoxicity. The total cumulative dose of liposomal doxorubicin is similar to doxorubicin (550 mg/m^2; 400 mg/m^2 for patients who have received radiation to the mediastinal area or concomitant cardiotoxic therapy). Cardiac function should be monitored with

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