WARNING

1. Severe local tissue necrosis will occur if there is extravasation during administration (see DOSAGE AND ADMINISTRATION). Doxorubicin must not be given by the intramuscular or subcutaneous route.

2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m² of doxorubicin, 3 to 5% at a dose of 400 mg/m², 5 to 8% at 450 mg/m² and 6 to 20% at 500 mg/m². The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400 mg/m². Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. Pediatric patients are at increased risk for developing delayed cardiotoxicity.

3. Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) has been reported in patients treated with anthracyclines, including doxorubicin (see ADVERSE REACTIONS). The occurrence of refractory secondary AML or MDS is more common when anthracyclines are given in combination with DNA-damaging anti-neoplastic agents or radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when dosages of anthracyclines have been escalated. The rate of developing secondary AML or MDS has been estimated in an analysis of 8638 patients with early breast cancer treated in 6 studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including NSABP B-15. Patients in these studies received standard doses of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant chemotherapy and were followed for 61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11 cases of AML or MDS were identified, for an incidence of 0.32 cases per 1000 patient years (95% CI 0.16 to 0.57) and a cumulative incidence at 5 years of 0.31% (95% CI 0.11 to 0.41%). In another analysis of 1474 patients with breast cancer who received adjuvant treatment with doxorubicin-containing regimens in clinical trials conducted at University of Texas M.D. Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In both experiences, patients who received regimens with higher cyclophosphamide dosages, who received radiotherapy, or who were aged 50 years or older had an increased risk of secondary AML or MDS. Pediatric patients are also at risk of developing secondary AML.

4. Dosage should be reduced in patients with impaired hepatic function.

5. Severe myelosuppression may occur.

6. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibacterial isolated from cultures of Streptomyces peucetius var. caesus. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine.

Chemically, doxorubicin hydrochloride is: C27H29NO11 •HCl 579.99

[(3-Amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)-oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride [25376-40-9].

The structural formula is as follows:

\[
\text{C}_{27}\text{H}_{29}\text{NO}_{11} \cdot \text{HCl}
\]

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophobic center. The molecule is amphoretic, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins.

Doxorubicin hydrochloride injection is a sterile, isotonic, preservative-free solution for intravenous use. It is available in 5 mL (10 mg), 10 mL (20 mg) and 25 mL (50 mg) single dose vials and 100 mL (200 mg) multiple dose vials. Each mL contains: Doxorubicin hydrochloride 2 mg; sodium chloride 9 mg for isotonicity; Water for injection q.s. Hydrochloric acid and sodium hydroxide may have been added for pH adjustment (2.5-4.5).

CLINICAL PHARMACOLOGY

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane binding, binding properties of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytotoxic activity.

Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generates highly reactive species including the hydroxyl free radical OH-. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level.

Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetics

Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multigagent therapy. It is shown that doxorubicin follows a multistep disposition after intravenous injection. In four patients, doxorubicin has demonstrated dose-independent pharmacokinetics in the dose range of 30 to 70 mg/m².

Distribution

The initial distribution half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volume ranges from 809 to 1214 L/m² and is indicative of extensive drug uptake into tissues. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin up to 1.1 mcg/mL.

Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.4-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m²
of doxorubicin given as a 15-minute intravenous infusion and 100 mg/m² of cisplatin as a 26-hour infusion. The peak concentration of doxorubicin in milk at 24 hours was 0.11 mcg/mL and AUC up to 24 hours was 9.3 mcg hr/mL while the AUC for doxorubicin was 5.4 mcg/hr/mL.

Doxorubicin does not cross the blood brain barrier.

Metabolism

Enzymatic reduction at the 7 position and cleavage of the sugar moieties which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxicity of doxorubicin. The disposition of doxorubicin (DOX-OL) in patients is formation rate limited, with the terminal half-life of DOX-OL ranging from 34 to 136 days. The disposition of doxorubicin, including the potential exposure of DOX-OL, i.e., the ratio between the AUC of DOX-OL and the AUC of doxorubicin, compared to ranges found for 0.4 and 0.6.

Excretion

Plasma clearance is in the range 324 to 809 mL/min/m² and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 2 to 12% of the drug and its metabolites appear in the urine during the same time period. In elderly, <3% of the dose was recovered as DOX-OL over 7 days.

Systemic clearance of doxorubicin is significant, due to a higher loss of drug with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in the volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight.

Pharmacokinetics in Special Populations

Pediatric

Following administration of 10 to 75 mg/m² doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 ± 511 mL/min/m². Further analysis demonstrated that clearance increased in children greater than 2 years of age (1540 mL/min/m²) was increased compared with children younger than 2 years. Children younger than 2 years of age (813 mL/min/m²) was decreased compared with older children and approached a range of clearance values determined in adults.

Geriatric

While the pharmacokinetics of elderly subjects (>65 years of age) have been evaluated, no dosage adjustment is recommended based on age (see PRECAUTIONS, Geriatric Use).

Gender

A published clinical study involving 6 men and 21 women with no prior anthracycline therapy revealed that patients with higher median doxorubicin clearance in the men compared to the women (1088 mL/min/m² versus 433 mL/min/m²). However, the half-life of doxorubicin was longer in men compared to the women (54 versus 35 hours).

Race

The influence of race on the pharmacokinetics of doxorubicin has not been evaluated.

Hepatic Impairment

The clearance of doxorubicin and doxorubicinol was reduced in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Renal Impairment

The influence of renal function on the pharmacokinetics of doxorubicin has not been evaluated.

CLINICAL STUDIES

The effectiveness of doxorubicin-containing regimens in the adjuvant therapy of early breast cancer has been primarily established based on data collected in a meta-analysis published in 1994 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG). The EBCTCG obtains primary data on all relevant studies, both published and unpublished, for early stage breast cancer and regularly updates these analyses. The principal endpoints for the adjuvant chemotherapy trials were disease-free survival (DFS) and overall survival. The EBCTCG has published comparisons of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to doxorubicin and/or other anthracyclines and anthracenediones; or hypersensitivity to doxorubicin, or any of its derivatives, or other anthracyclines or anthracenediones, (see WARNINGS AND DOSAGE AND ADMINISTRATION).

WARNINGS

Doxorubicin should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin. Also, pre-existing treatment with doxorubicin should be preceded by a careful baseline assessment of blood counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function (as assessed by left ventricular ejection fraction (LVEF). Patients should be carefully monitored during treatment for possible cardiac complications due to myelosuppression. Supportive care may be necessary for the treatment of severe neutropenia and severe infectious complications. Monitoring for potential cardiotoxicity is also important, especially with greater cumulative exposure to doxorubicin. Doxorubicin may potentiate the toxicity of other anticancer therapies (see PRECAUTIONS, Drug Interactions).

Cardiac Function

Cardiotoxicity is a known risk of anthracycline treatment. Anthracycline-induced cardiotoxicity may be manifested by early (or acute) and late (delayed) events. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and electrocardiogram changes such as specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and bundle branch block have also been reported. These effects do not usually predict any subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not considered an indication for the suspension of doxorubicin treatment.

Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Cardiomyopathy is manifested by a reduction in LV systolic function or signs and symptoms of congestive heart failure (CHF) such as tachycardia, dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, pericardial effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening cardiomyopathy is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug. The probability of developing impaired myocardial function, based on a combined index of signs and symptoms and depressed ejection fraction (LVEF) is estimated to be 2% at a total cumulative dose of 300 mg/m² of doxorubicin, 3% to 5% at a dose of 400 mg/m², 5% to 8% at a dose of 450 mg/m² and 6% to 20% at a...
gestive heart failure was reported to be 5/168 (3%) prospective review, the probability of developing con-
bolus injection once every 3 weeks. In a retro-
creasing total cumulative doses of doxorubicin.
chance of developing CHF increases rapidly with
risk of developing CHF is related to the dose of doxorubicin.
doxorubicin cardiotoxicity. The total dose of doxorubicin adminis-
ted to an individual patient also takes into account previous or concomitant

Cardio Toxicity may occur at lower doses in pediatric patients. Although mediatinal irradiation, concomitant use of other cardiotoxic drugs, doxorubicin exposure at an early age, and advanced age appear to be risk factors that hasten heart disease as a co-factor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may be significant at doses lower than the recommended cumulative dose of doxorubicin. Studies have suggested that concomitant admin-
istration of digitalis, diuretics, and afterload reducers may increase the risk of doxorubicin cardiotoxicity.

Hematologic Toxicity
As with other cytotoxic agents, doxorubicin may produce myelosuppression. Myelosuppression requires care in patient selection and differential WBC, red blood cell (RBC), and platelet counts should be assessed before and during each cycle of therapy with doxorubicin. A dose-dependent, reversible leukopenia and/or granulo-
cyopenia (neutropenia) are the predominant manifestations of doxorubicin hematologic tox-
icity and is the most common acute dose-limiting toxicity of doxorubicin. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir 10 to 14 days after treatment with recovery usually occurring by the 21st day. Thrombocytopenia may also occur.

Secondary Leukemia
The occurrence of secondary AML or MDS has been reported most commonly in patients treated with chemotherapy regimens containing anthracy-
cines (including doxorubicin) and DNA-dam-
aging antineoplastic agents, in combination with radiotherapy. In patients heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Such cases generally occur in the late remission period. The rate of developing secondary AML or MDS has been estimated in an analysis of 8563 patients and was higher in patients who had received anthracyclines (including doxorubicin) as compared to other groups (0.32 cases per 1000 patient years (95% CI 0.16 to 0.57) and a cumulative incidence at 5 years of 0.21% (95% CI 0.01 to 0.41). In another analy-

Hepatic Impairment
Pediatric patients are also at risk of develop-
ing secondary AML.

Effects at Site of Injection
Phlebitis may occur from an injection into a small vessel resulting in localized pain, swelling, and induration.

Extravasation
On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying local inflammatory reaction, even if blood returns well on aspiration of the infusion.

Hepatic Impairment
Since metabolism and excretion of doxorubicin occurs predominantly by the liver, the toxicity of recommended doses of doxorubicin can be enhanced by hepatic impairment; therefore, prior to the initial evaluation of hepatic function is recommended using con-

Drug Interactions
Doxorubicin is emetogenic. Antiemetics may reduce the incidence of vomiting. Prophylactic use of antiemetics should be considered before admin-
istration of doxorubicin, particularly when given in combination with other emetogenic drugs.

Information for Patients
Patients should be informed of the expected adverse effects of doxorubicin, including gastro-intestinal symptoms (nausea, vomiting, diar-
hea, and stomatitis) and potential neurotropic complications. Patients should consult their physician if vomiting, diarrhea, or fever of in-
dence of infection, symptoms of CHF, or injec-
tion-site pain occurs following therapy with doxorubicin. Patients should be informed that they will almost certainly develop alopecia. Patients should be advised that their urine may appear reddish or brown for 1-2 days after doxorubicin and that they should not be alarmed.

Pregnancy Category D
This compound is teratogenic and embryotoxic at doses of

Paclitaxel
There have been a number of reports in the liter-

Cyclosporine
The metabolism of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicin. Literature reports

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The metabolism of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicin. Literature reports
suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than doxorubicin alone. Other adverse reactions have also been described.

Dexrazoxane

In a clinical study of women with metastatic breast cancer, the concurrent use of the cardio-pulmonary effects of doxorubicin with a regimen of fluorouracil, doxorubicin, and cyclophosphamide was associated with a lower tumor response rate. Later initiation of dexra-

zoxane (after administration of a cumulative dose of 300 mg/m² of doxorubicin had been given as a component of FAC) was not asso-
ciated with a reduction in chemotherapy activity. Dexra-

zoxane has been indicated for use in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and continuing with doxorubicin therapy.

Cytarabine

Necrotizing colitis manifested by typhilitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin given by intravenous push daily for 5 days and cytarabine given by continuous infusion daily for 7 or more days.

Cyclophosphamide

The addition of cyclophosphamide to doxorubicin treatment does not affect exposure to doxorubicin, but may result in an increase in exposure to the metabolite, acrolein. Doxorubicin also has 5% of the cytotoxic activity of doxorubicin. Concurrent treatment with doxorubicin has been shown to result in decreased cyclophos-

phamide-induced hemorrage in cystic aclys. Acute myeloid leukemia has been reported as a second malignancy after treatment with doxorubicin and cyclophosphamide.

Adverse Reactions

Doxorubicin has been associated with several adverse reactions. These include cardiotoxicity, hematologic toxicity, gastrointestinal toxicity, skin toxicity, and potential for myelosuppression and gonadal impairment.

Cardiotoxicity

Doxorubicin is known to cause cardiac toxicity, particularly in patients receiving high cumulative doses. This toxicity may be dose-dependent and may occur with doses as low as 300 mg/m². Cardiac toxicity can manifest as ECG changes, left ventricular dysfunction, and congestive heart failure. Long-term follow-up studies have shown that even with reduced-dose regimens, the risk of cardiac toxicity remains.

Hematologic Toxicity

Doxorubicin can cause myelosuppression, leading to decreased white blood cell (WBC) counts, platelet counts, and hemoglobin levels. This can result in an increased risk of infections and bleeding complications. Regular monitoring of blood counts is important to detect and manage these toxicities.

Gastrointestinal Toxicity

Doxorubicin can cause mucositis, nausea, vomiting, and diarrhea. These symptoms are dose-dependent and can be severe. Gastrointestinal toxicity may require the use of supportive care, including hydration, oral rehydration solutions, and antiemetics.

Skin Toxicity

Doxorubicin can cause dermatologic toxicities, including alopecia, skin rash, and severe hyperpigmentation. Alopecia is a common side effect, and the risk of permanent hair loss can be managed with specific hair care techniques. Skin rashes may also occur and can range from mild erythema to severe exfoliative dermatitis.

OVERDOSAGE

Acute overdose with doxorubicin enhances the toxic effect of mucositis, leukopenia, and thrombocytopenia. Treatment of acute overdose consists of treatment of mucositis. Severe cases of mucositis may require hospitalization with antibiotic and antifungal therapy, platelet transfusions, and symptomatic treatment of mucositis. Use of hematopoietic growth factor (CSF, GM-CSF) may be considered. The 100 μL (2 mg/mL) doxorubicin 10% injection dose may be a single dose vial and caution should be taken to prevent inadvertent overdose. Cumulative doses of doxorubicin increase the risk of cardiomyopathy and resultant congestive heart fail-

Hematologic (See WARNINGS.)

Hypersensitivity

Fever, rash, and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to imipenem has been reported.

Neurological

Peripheral neuropathy in the form of local- regimen sensory and/or motor disturbances have been reported in patients treated intra-arterially with doxorubicin, mostly in combination with cisplatin. Animal studies have shown seizures and coma in rodents and dogs treated with intra-carotid doxorubicin. Seizures and coma have been reported in patients treated with doxorubicin in combination with cisplatin or vincristine.

Ocular

Conjunctivitis, keratitis, and lacrimation occur rarely.

Other

Malaise/asthenia have been reported.

Adverse Reactions in Patients with Early Breast Cancer Receiving Doxorubicin-Containing Adjuvant Therapy

Safety data were collected from approximately 2300 women who participated in a randomized, open-label trial (NSABP B-15) evaluating the use of AC versus CMF in the treatment of early breast cancer involving axillary lymph nodes. In the safety analysis, the follow-up data from all patients receiving AC were combined (N=739 evaluable patients) and compared with data from patients receiving conventional CMF (i.e., oral cyclophosphamide; N=739 evaluable patients). The most relevant adverse events reported in this study are provided in Table 2.

Table 2. Relevant Adverse Events in Patients with Early
cancer Receiving 

AC* | Conventional 
cancer

<table>
<thead>
<tr>
<th>Treatment administration</th>
<th>N=1492</th>
<th>N=739</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of cycles</td>
<td>3.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Total cycles</td>
<td>5676</td>
<td>4068</td>
</tr>
<tr>
<td>Adverse events, % of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>16.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Rash</td>
<td>7.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>9.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Gastrointestinal Toxicity</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Weight loss</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Weight gain</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Total treatment-related death</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Includes pooled data from patients who received either AC alone or AC followed by 3 cycles of CMF.
DOSAGE AND ADMINISTRATION: Care in the administration of doxorubicin will reduce the incidence of perivenous infiltration (see WARNINGS). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if it is observed well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection of the drug should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min, q.d. x 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m² as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration.

Doxorubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m² given as a single intravenous injection every 21 to 28 days.

In a large randomized study (NSABP B-15) of patients with early breast cancer involving axillary lymph nodes (see CLINICAL PHARMACOLOGY, CLINICAL STUDIES and ADVERSE REACTIONS, Adverse Reactions in Patients with Early Breast Cancer Receiving Doxorubicin-Containing Adjuvant Therapy), the combination dosage regimen of AC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²) was administered intravenously on day 1 of each 21-day treatment cycle. Four cycles of treatment were administered.

Dose Modifications

Patients in the NSABP B-15 study could have dose modifications of AC to 75% of the starting doses for neutropenic fever/infection. When necessary, the next cycle of treatment cycle was delayed until the absolute neutrophil count (ANC) was >1000 cells/mm³ and the platelet count was ≥100,000 cells/mm³ and nonhematologic toxicities had resolved.

Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

<table>
<thead>
<tr>
<th>Plasma bilirubin concentration (mg/dL)</th>
<th>Dosage reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 to 3</td>
<td>50</td>
</tr>
<tr>
<td>3.1 to 5</td>
<td>75</td>
</tr>
</tbody>
</table>

Reconstitution Directions

It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. The tubing should be attached to a butterfly needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised vascularity or hypovolemia. The rate of administration is dependent on the size of the vein, and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Locoregional, hematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Contact with saline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Handling and Disposal

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.¹ There is no general agreement that all the procedures recommended in these guidelines are necessary or appropriate. However, given the toxic nature of this substance, the following protective recommendations are provided:

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: gowns, gloves and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelids(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient’s urine and other body fluids for at least 5 days after each treatment.

HOW SUPPLIED:

Doxorubicin Hydrochloride Injection, USP, 2 mg/mL, a sterile product which contains no preservatives, is available as follows:

<table>
<thead>
<tr>
<th>Product NDC No.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>88305 63323-883-05</td>
<td>Doxorubicin hydrochloride 10 mg in a 5 mL single dose vial, packaged individually.</td>
</tr>
<tr>
<td>88310 63323-883-10</td>
<td>Doxorubicin hydrochloride 20 mg in a 10 mL single dose vial, packaged individually.</td>
</tr>
<tr>
<td>88330 63323-883-30</td>
<td>Doxorubicin hydrochloride 50 mg in a 10 mL single dose vial, packaged individually.</td>
</tr>
<tr>
<td>100161 63323-101-61</td>
<td>Doxorubicin hydrochloride 200 mg in a 100 mL multiple dose vial, packaged individually.</td>
</tr>
</tbody>
</table>

Store refrigerated, 2° to 8°C (36° to 46°F).

PROTECT FROM LIGHT.

Retain vial in carton until time of use. Preservative Free. Discard unused portion.

Vial stoppers do not contain natural rubber latex.

REFERENCES:


