

Data Sheet

ONKOTRONE

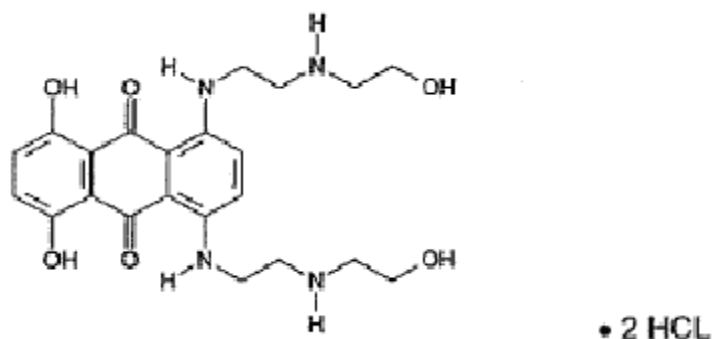
Mitozantrone Hydrochloride

Name of Drug

Mitozantrone (as Hydrochloride)

Description

Mitozantrone hydrochloride is a synthetic anthracenedione. The chemical name is 1,4-dihydroxy-5,8-bis-[2-(2-hydroxyethylamino)-ethylamino]-9,10-anthraquinone dihydrochloride, and the chemical structure is as follows:



The molecular formula is $C_{22}H_{28}N_4O_6 \cdot 2HCl$, and the molecular weight is 517.4. The CAS No. is 70476-82-3. Mitozantrone hydrochloride is a hygroscopic dark blue solid.

ONKOTRONE Concentrated Injection is a clear, dark blue liquid with a pH of 3.0-4.5. One mL of the solution for injection contains 2.328 mg mitozantrone hydrochloride (equivalent to 2 mg mitozantrone), with sodium chloride, sodium acetate, acetic acid-glacial and water for injection as excipients.

PHaRMACOLoGY

Mitozantrone hydrochloride is a cytostatic agent that has shown substantial anti-tumor activity in the treatment of a variety of tumors. It is a DNA-reactive agent, but the precise mechanism of the tumor destroying effect has not yet been completely elucidated.

Mitozantrone acts both on proliferating and non-proliferating cells. It is a cell cycle (phase) non-specific substance.

The main toxic effects of mitozantrone in animals at doses within the human therapeutic range are reversible myelosuppression (predominantly leucopenia, with anaemia and thrombocytopenia being less severe) and lymphocytic depletion of the lymphoid organs. In continuous daily dosage schedules, gastrointestinal haemorrhage and congestion were observed, but these were not seen in intermittent schedules as used clinically. Studies in dogs using mitozantrone in combination with other antineoplastic agents indicated that additive myelosuppression might be expected from combination therapy. Toxicological tests have been carried out with mitozantrone in order to study its cardiotoxic effects. In studies in dogs and monkeys, doxorubicin given at equileucopenic doses was used as a positive control for anthracycline-induced cardiomyopathy. Dogs given mitozantrone and untreated control dogs showed slight dilatation of the sarcoplasmic reticulum, which regressed over time. In monkeys, clinical signs of congestive heart failure were observed in animals given doxorubicin but not in those given mitozantrone. In the doxorubicin-treated monkeys, myocyte changes were characteristic of degeneration, while the myocyte changes in monkeys given mitozantrone suggested cellular regeneration and repair. In rats, there was no evidence of the progressive cardiomyopathy characteristic of anthracyclines.

Pharmacokinetics

Mitozantrone is rapidly eliminated from blood plasma after intravenous application and is extensively distributed to tissues (apart from the CNS) and has therefore a large distribution volume. A triphasic plasma clearance is observed. Elimination is slow with a terminal half-life of over 12 days (range 5-18). Administration schedules of daily for 5 days and a single dose every 3 weeks resulted in similar estimates of the half-life. Plasma accumulation of drug was not apparent on either schedule. Excretion by the biliary and faecal route appears to be the major pathway of elimination for mitozantrone. The renal excretion is of secondary importance; only 6-11% of the dose is recovered in the urine within 5 days after the drug administration, with 65% of this being unchanged mitozantrone. The remaining 35% consisted primarily of two inactive metabolites, the mono- and di-carboxylic acid derivatives and their glucuronide conjugates. One study found that a mean of 18.3% (13.6 - 24.8%) of a dose of ¹⁴C-labelled mitozantrone was excreted via the faeces over 5 days. Mitozantrone does not cross the blood brain barrier or the placental barrier. Distribution into testes is relatively low. One study found that the protein binding of mitozantrone was 78% at concentrations ranging from 26 to 455 ng ¹⁴C-mitozantrone/mL pooled human plasma. The extent of binding was independent of concentration. No significant difference in the pharmacokinetics of mitozantrone was observed in patients with moderately impaired hepatic function (serum bilirubin 1.3 to 3.4 mg/dL) as compared to 16 patients without hepatic dysfunction. Studies in 4 patients with severe hepatic impairment (bilirubin greater than 3.4 mg/dL) suggest that these patients have a lower total body clearance and a larger area under the curve (AUC) than other patients receiving a comparable dose. In animals, pharmacokinetic studies

with radiolabelled mitozantrone indicate rapid, doseproportional distribution into most tissues. Biliary excretion is the major route of elimination, with the urine and bile of the rat containing the same metabolites as those present in human urine. There is no significant absorption of mitozantrone in animals following oral administration.

Indications

ONKOTRONE is indicated for the treatment of:

- Locally advanced or metastatic carcinoma of the breast
 - Non-Hodgkin's lymphoma
 - Adult acute non-lymphocytic leukaemia (ANLL)
 - Chronic myelogenous leukaemia in blast crisis
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Contraindications

- Known hypersensitivity to mitozantrone
 - Pregnancy, lactation
 - Severe myelosuppression due to previous treatment with other cytotoxic agents or radiotherapy: treatment with mitozantrone should not be initiated until bone marrow has recovered
 - Patients who have received prior substantial anthracycline therapy with abnormal cardiac function prior to the initiation of therapy (see Precautions)
 - Severe hepatic impairment.
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Precautions

General

ONKOTRONE should be administered only under the supervision of a doctor experienced in the use of cancer chemotherapy.

Myelosuppression

Since ONKOTRONE causes a high incidence of myelosuppression, it should be used with caution in patients in poor general condition, patients with pre-existing myelosuppression due to any cause, or patients with severe infections at the florid stage. The haematological blood parameters must be monitored before each application of ONKOTRONE as well as at least once during each treatment cycle.

Following recommended doses, leucopenia is usually transient, with the nadir at about 10 days after dosing and recovery usually occurring by the twenty-first day. White blood

cell counts of 1500 cells/mm³ may be expected, but they really fall to below 1000 cells/mm³ at recommended dosages. Red blood cells and platelets should also be monitored, as these may also be reduced. Haematological toxicity may require reduction of dose or suspension or delay of ONKOTRONE therapy.

Cardiac Changes

Cases of functional cardiac changes, including congestive heart failure and decreases in left ventricular ejection fraction have been reported during ONKOTRONE therapy. These events have most commonly occurred in patients with a history of severe heart disease, prior treatment with anthracyclines, and/or prior mediastinal irradiation. In patients with one or more of these risk factors, or in the case of combination of ONKOTRONE with other cardiotoxic drugs, the treatment must be carefully monitored, with regular controls of cardiac function, and adjustment of the dose where necessary.

When a total cumulative mitozantrone dose of 160 mg/m² has been reached in patients with no risk factors, regular control of cardiac function should be carried out.

Patients with cardiac insufficiency generally respond well to supportive treatment with digitalis and/or diuretic agents.

Intrathecal Use

Safe use of ONKOTRONE intrathecally has not yet been established.

Other Precautions

Hyperuricaemia may occur as a result of rapid lysis of tumor cells by ONKOTRONE. Serum uric acid levels should be monitored and hypouricaemic therapy instituted prior to the initiation of antileukaemic therapy.

Systemic infections should be treated concomitantly with, or just prior to, commencing therapy with ONKOTRONE.

Doses greater than 140 mg/m² are not recommended, particularly as a single bolus injection. Such administrations have caused fatal overdose as a result of severe leucopenia and infection.

See also Pharmaceutical Precautions below.

Impaired Renal Function

Patients with severe renal failure have not been studied. However, as mitozantrone undergoes limited renal excretion and extensive tissue binding, it is unlikely that the therapeutic effect or toxicity in these patients would be reduced by peritoneal dialysis or

haemodialysis. ONKOTRONE should be used with caution in patients with severe renal insufficiency.

Impaired Hepatic Function

Although adequate data on the use of mitozantrone in patients with hepatic dysfunction are not yet available, the pharmacokinetic profile suggests that clearance of the drug in such patients may be reduced and dosage may need to be adjusted accordingly. ONKOTRONE should be used with caution in patients with severe hepatic insufficiency. Liver function should be monitored regularly before and during treatment.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a lifetime study in rats, there was a possible association between the administration of mitozantrone and the development of malignant neoplasia.

Mitozantrone caused point mutations, DNA damage and sister chromatid exchanges *in vitro*. Lifetime studies in mice and rats showed no residual clastogenic effect. Mitozantrone did not induce cell transformation in mammalian cells *in vitro*.

The effects of mitozantrone on human fertility have not been established. No adequate studies have been conducted in animals to determine the effect of mitozantrone on fertility.

Use in Pregnancy (Category D)

The effects of mitozantrone on human pregnancy have not been established. As with other antineoplastic agents, patients and their partners should be advised to avoid conception for at least six months after cessation of therapy. ONKOTRONE should not be administered to patients who are pregnant.

Animal studies have not demonstrated teratogenic activity due to mitozantrone treatment. Decreased foetal bodyweight noted in high dose rats (0.2 mg/kg/day) and an increased incidence of premature delivery noted in rabbits (0.01 to 0.05 mg/kg/day) were attributed to maternal toxicity.

Use in Lactation

Mitozantrone is excreted in human milk and significant concentrations (18 nanogram/mL) have been reported for 28 days after last administration. Because of the potential for serious adverse reactions in infants from mitozantrone, breastfeeding should be discontinued before starting treatment.

Use in Children

Experience in paediatrics patients is limited.

Interactions

When used in combination with other antineoplastic agents, more potent toxic effects, especially an increased myelotoxic and cardiotoxic effect are expected.

When used in combination regimens, the initial dose of ONKOTRONE should be reduced by 2-4 mg/m² below the dose recommended for single-agent usage.

Instructions to Patients

Patients should be advised to expect a blue-green colouration to the urine for 1-2 days after ONKOTRONE administration. Bluish discolouration of the sclera may also occur.

Patients should be instructed to inform their doctor of any prior abnormal heart conditions.

Patients should also be advised of the signs and symptoms of myelosuppression.

Adverse Reactions

When used as a single injection every three weeks in the treatment of solid tumors and lymphomas, the most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild and transient. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy.

In patients with leukaemia, the pattern of side effects is generally similar, although there is an increase in both frequency and severity, particularly of stomatitis and mucositis. Nevertheless, overall, patients with leukaemia tolerate treatment with ONKOTRONE well.

More Common Reactions

Gastrointestinal: Nausea, vomiting, stomatitis and/or mucositis. These are mostly of mild-moderate severity and transient. In some cases the stomatitis and mucositis may be more frequent and pronounced during the treatment of leukaemia.

Dermatological: Alopecia, usually mild and reversible on discontinuation of treatment.

Haematological: Myelosuppression, particularly leucopenia (see Precautions). Thrombocytopenia and anaemia are less common.

Renal: Mitozantrone injection may impart a blue-green colour to the urine for 1-2 days after administration.

Less Common Reactions

Gastrointestinal: Diarrhoea, constipation, anorexia, gastrointestinal bleeding, abdominal pain, altered taste.

Respiratory: Dyspnoea.

Local: Phlebitis. Tissue necrosis following extravasation has been reported rarely.

General: Fever, fatigue and weakness, and nonspecific neurological side effects. Hypersensitivity reactions.

Dermatological: Rash, nail pigmentation.

Hepatic: Increased liver enzyme levels and elevated bilirubin levels have been reported occasionally.

Renal: Elevated serum creatinine and blood urea nitrogen levels have been reported occasionally.

Ophthalmic: Reversible blue colouration of the sclerae has been reported.

Severe or Life-Threatening Reactions.

Cardiovascular: Cardiovascular effects include decreased left ventricular ejection fraction (determined by ECHO or MUGA scan), ECG changes and acute arrhythmia. Congestive heart failure has been reported. Such cases have generally responded well to treatment with digitalis and/or diuretics. In patients with leukaemia there is an increase in the frequency of cardiac events. The direct role of mitozantrone in these cases is difficult to assess, since some patients had received prior therapy with anthracyclines and since their clinical course is frequently complicated by anaemia, fever, sepsis and intravenous fluid therapy.

Myelosuppression: Some degree of leucopenia is to be expected following recommended doses of ONKOTRONE in solid tumors; however, suppression of white blood cell counts below 1,000/mm³ is infrequent. With dosing every 21 days, leucopenia is usually transient, reaching its nadir at about ten days after dosing, with recovery usually occurring by the twenty-first day. Thrombocytopenia can occur and anaemia occurs less frequently. Myelosuppression may be more severe and prolonged in patients with solid tumors, who have had extensive prior chemotherapy or radiotherapy, or in debilitated patients.

Overdosage

Symptoms

In the case of acute or chronic over dosage, the observed side effects are amplified. The extent of bone marrow depression, at the extreme agranulocytosis accompanied by

necrotising angina and critical thrombocytopenia, determines the further course in acute and chronic overdosage. Ulceration of the mouth and gastrointestinal tract, haemorrhagic enterocolitis with massive bleeding, diarrhoea and persistent signs of renal and hepatic toxicity can occur.

If aplasia of the bone marrow occurs as a result of acute over dosage with mitozantrone, it will, from existing experience, persist longer (approx 3 weeks).

In patients with acute leukaemia, it can result in pronounced stomatitis in isolated cases. Appropriate measures for prophylaxis and treatment should therefore be taken.

In isolated cases, acute cardiac symptoms of different severity are possible.

Toxicity may be delayed and life-threatening e.g. myelosuppression.

Treatment

A specific antidote to mitozantrone is not known. Mitozantrone is rapidly eliminated from the blood plasma and shows high tissue affinity. Therefore, it cannot be eliminated by dialysis. Haematological support may be required during prolonged periods of bone marrow depression, and infection prophylaxis with antibiotics may be required. The usual supportive measures (maintenance of fluid and electrolyte balance, monitoring of renal and hepatic functions, strict cardiovascular monitoring etc) should be carried out. Every overdosage requires careful monitoring of the clinical findings to identify possible delayed complications.

Dosage and Administration

The dose should be adjusted to each patient carefully.

Carcinoma of the breast, non-Hodgkin's lymphoma

Single-agent therapy: During monotherapy, a dose of 14 mg mitozantrone/m² of body surface area, given as a single intravenous dose, is recommended as the initial dose for the first cycle. This dose can be repeated after 21 days.

In patients with diminished bone marrow reserves as a result of previous radiation and/or chemotherapy or those in a general poor state of health, the initial dose should be reduced to 12 mg/m² or less, corresponding to the haematological parameters.

For each repeated application of mitozantrone, the dose should be determined by clinical judgment, depending on the extent and duration of myelosuppression.

The following general recommendations can be given:

Lowest value (nadir) of leucocytes and thrombocytes (cell/mm³)	Time to recovery	Subsequent dosing
>1500 leucocytes and >50,000 (cells/mm ³) thrombocytes	21 days or less	As previous dose or increase by 2 mg/m ² if the degree of myelosuppression indicates that a higher dose can be tolerated
>1500 leucocytes and >50,000 thrombocytes	More than 21 days	Wait for return to normal, and then as previous dose
<1500 leucocytes or <50,000 thrombocytes	Any duration	Reduction of the previous dose by 2 mg/m ² after recovery of blood counts
<1000 leucocytes or <25,000 thrombocytes	Any duration	Reduction of the previous dose by 4 mg/mg ² after recovery of blood counts

Combination Therapy: Mitozantrone has been given in various combination regimens with the following cytotoxic agents for the treatment of breast cancer and lymphomas: cyclophosphamide, fluorouracil, vincristine, vinblastine, bleomycin, methotrexate (standard dose or 200 mg/m² with leucovorin rescue) and glucocorticoids.

For the combination of mitozantrone with other myelosuppressive agents, it is advisable to reduce the initial dose of mitozantrone recommended for monotherapy by 2 to 4 mg mitozantrone/m² of body surface area. In further treatment cycles, the mitozantrone dose should be similarly tailored to individual progress and to the duration and degree of myelosuppression.

Long-term survival data for non-Hodgkin's lymphoma are as yet inadequate to establish comparability between combinations containing mitozantrone and similar combinations containing doxorubicin.

Leukaemia

Combination Therapy: Mitozantrone, together with cytosine arabinoside, has been used successfully for the treatment of both first and second line patients with acute non-lymphocytic leukaemia. For induction, the recommended dose is 10 to 12 mg/m² mitozantrone for three days and 100 mg/m² of cytosine arabinoside for 7 days (the latter given as a continuous 24 hr infusion).

If a second course is indicated, then this is given with the same combination at the same daily dosage levels but with the mitozantrone given for only 2 days and cytosine arabinoside for only 5 days.

If severe or life-threatening non-haematological toxicity is observed during the first induction course, the second induction course should be withheld until the toxicity clears.

Paediatric Usage: Experience in paediatric patients is limited.

Single agent dosage for acute non-lymphocytic leukaemia or chronic myelogenous leukaemia in blast crisis: The recommended dose for induction is 12 mg/m² of body surface area, given as a single intravenous dose daily for 5 consecutive days (total 60 mg/m²). In clinical studies, with this dosage regimen, patients who achieved a complete remission did so with the first induction course.

Re-induction upon relapse may be attempted with mitozantrone using the same dose regimen.

Directions for Use

ONKOTRONE vials contain an overage to allow for withdrawal of the required volume.

ONKOTRONE should be diluted to at least 50 mL with either sodium chloride for injection or 5% glucose for injection. This solution should be introduced slowly into the tube of a freely running intravenous infusion of sodium chloride for injection or 5% glucose for injection over not less than 3-5 minutes. Administration should be followed with a flush of the appropriate diluent.

If extravasation occurs, the administration should be stopped immediately and restarted in another vein.

Pharmaceutical Precautions

Care should be taken to avoid contact of ONKOTRONE with the skin, mucous membranes or eyes. The use of goggles, gloves and protective gowns is recommended during preparation and administration. To reduce the possibility of spillages and splashes when removing ONKOTRONE from the vial, it is recommended that a 20 gauge needle, or one with a narrower bore, be used.

ONKONTRONE can cause staining.

Skin accidentally exposed to ONKOTRONE should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used. Equipment and spills on environmental surfaces may be cleaned up by using an aqueous solution of calcium hypochlorite (5.5 parts calcium hypochlorite in 13 parts by weight of water for each 1 part by weight of ONKOTRONE). Absorb the remaining solutions with gauze or towels and dispose of these in a safe manner. Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite solutions.

ONKOTRONE does not contain an antimicrobial preservative. Although the preparation itself does have some antimicrobial efficacy, the injection should be used as soon as possible after opening and any residue discarded.

ONKOTRONE must not be mixed in the same infusion as heparin since a precipitate may form. It is recommended that ONKOTRONE not be mixed in the same infusion with other drugs as specific compatibility data are not available.

Presentation

Vials: 10 mg/5 mL, 20 mg/10 mL, 25 mg/12.5 mL, 30 mg/15 mL.

Storage

Unopened Vials: Store below 25°C. Do not freeze. Protect from light.

Shelf-life: 3years.

After Reconstitution: Potency is maintained for 2 days; however, to reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.

Medicine Classification

Prescription Medicine

Name and Address

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Date of Preparation

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ONKOTRONE is a trademark of Baxter Healthcare S.A.