Mitomycin is used, with other antineoplastic agents, in the treatment of many solid tumours including those of the bladder, breast, cervix, eye, liver, lung, stomach, and prostate as indicated by the cross-references given below. Mitomycin has been tried in other neoplasms including those of the gastrointestinal tract, head and neck, pancreas, in melanoma, sarcomas, and in leukaemias.

Dosage regimens include an initial dose of 10 to 20 mg/m^2 intravenously; subsequent doses are repeated at intervals of 6 to 8 weeks if blood counts permit, and should be reduced according to the previous haematological response. Another suggested regimen is 2 mg/m^2 daily for 5 days, repeated after 2 days. Other regimens may be used, particularly in combination.

Doses are adjusted according to the effect on bone marrow and treatment should not be repeated until the leucocyte and platelet counts are above acceptable levels (see also Bone-marrow Depression, p.639).

Mitomycin is also used as a bladder instillation: 10 to 40 mg is instilled once weekly or three times a week for a total of 20 doses in the treatment of superficial bladder tumours. For the prevention of recurrent bladder tumours 20 mg may be instilled every 2 weeks, or 40 mg monthly or 3-monthly. Alternatively 4 to 10 mg may be instilled once weekly or three times a week. These doses are usually given in 10 to 40 mL of water for injection. The solution should be retained in the bladder for at least 1 hour.

Mitomycin has been given by the intra-arterial route in the treatment of liver tumours, sometimes as an infusion of microcapsules designed to produce localised embolisation.

Mitomycin is used for its effect on fibroblasts to improve outcomes and reduce scarring in certain types of surgery, notably in glaucoma (see below).

◊ References.

1. Abraham LM, *et al.* Mitomycin: clinical applications in ophthalmic practice. *Drugs* 2006; **66:** 321–40.
2. Bolenz C, *et al.* Intravesical mitomycin C for superficial transitional cell carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 1273–82.
3. Tabaee A, *et al.* Mitomycin C and endoscopic sinus surgery: where are we? *Curr Opin Otolaryngol Head Neck Surg* 2007; **15:** 40–3.
4. Warner D, Brietzke SE. Mitomycin C and airway surgery: how well does it work? *Otolaryngol Head Neck Surg* 2008; **138:** 700–9.

Glaucoma. Mitomycin, like fluorouracil, is effective in improving the outcome of glaucoma filtering surgery in selected patients when used as an adjunct to prevent the formation of scar tissue (see p.1873). Fluorouracil is usually given as a regimen of multiple injections but mitomycin given as a single intra-operative topical application in usual concentrations ranging from 0.2 to 0.5 mg/mL appears to be of similar efficacy.[1,2] A systematic review of 11 studies concluded that intra-operative mitomycin reduced the chances of failure in high-risk patients, and in those having their first trabeculectomy.[3] However it was noted that the nature of the data might have led to overestimation of the effect and that there was some evidence of an increased risk of cataract with mitomycin. Late hypotony is also a problem.[4] For other potential complications see Effects on the Eye, above.

1. Skuta GL, *et al.* Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1992; **99:** 438–44.
2. Katz GJ, *et al.* Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery: extended follow-up. *Ophthalmology* 1995; **102:** 1263–9.
3. Wilkins M, *et al.* Intra-operative mitomycin C for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 25/04/06).
4. Bindlish R, *et al.* Efficacy and safety of mitomycin-C in primary trabeculectomy: five-year follow-up. *Ophthalmology* 2002; **109:** 1336–42.

Malignant neoplasms. Mitomycin is used in the prevention of recurrent bladder cancer (p.659), in the palliative therapy of advanced breast cancer (p.661), in malignancies of the cervix (p.663), eye (p.664), stomach and anus (p.664 and p.666), liver (p.667), and non-small cell lung cancer (p.668), and has been tried in advanced prostatic cancer (see p.671).

Pterygium. Pterygium is a degenerative condition of subconjunctival tissues that results in a vascularised overgrowth of the conjunctiva and cornea. It is cosmetically unappealing but does not usually require treatment. However, if it affects the pupillary area it can be treated surgically. Pterygium often recurs after removal and methods used to prevent recurrence include radiotherapy or the topical application of mitomycin or thiotepa.[1]

Thiotepa has been applied postoperatively as 0.05% eye drops for several weeks, but pterygium may still recur[2] and adverse effects include conjunctival injection, granuloma, hypertrophic conjunctiva, and black deposits in the conjunctival fornix.[1] Depigmentation of the eyelids may also be a problem, so patients should avoid direct sunlight during thiotepa use.[1]

Mitomycin has been applied topically to the surgical site, or given as eye drops postoperatively.[1] The optimal intra-operative exposure time and concentration are uncertain: concentrations of 0.02 or 0.04% have been applied for up to 5 minutes,[1,3] and low-dose treatment with mitomycin 0.02% for 30 seconds has been reported to be effective with few complications.[4] Postoperative treatment has generally been given as 0.02, 0.04, or 0.1% eye drops for up to 2 weeks, but the higher concentrations and longer treatment periods have been associated with more adverse effects,[1] some of which may be severe and sight-threatening (see also Effects on the Eyes, above). Comparisons of intra-operative with postoperative use suggest that pterygium recurrence rates are similar.[1,5]

A range of β-irradiation doses and fractionation methods have been used. Long-term complications include posterior subcapsular changes of the lens, atrophy and ulceration of the sclera, and scleral necrosis leading to endophthalmitis.[1] In one retrospective study,[6] intra-operative use of 0.04% mitomycin was more effective than β-irradiation in preventing recurrence after surgery. In another study,[7] postoperative mitomycin 0.02% for one week was less effective than radiation therapy.

1. Hoffman RS, Power WJ. Current options in pterygium management. *Int Ophthalmol Clin* 1999; **39:** 15–26.
2. Chapman-Smith JS. Pterygium treatment with triethylene thiophosphoramide. *Aust N Z J Ophthalmol* 1992; **20:** 129–31.
3. Anduze AL. Pterygium surgery with mitomycin-C: ten-year results. *Ophthalmic Surg Lasers* 2001; **32:** 341–5.
4. Cheng H-C, *et al.* Low-dose intraoperative mitomycin C as chemoadjuvant for pterygium surgery. *Cornea* 2001; **20:** 24–9.
5. Oguz H, *et al.* Intraoperative application versus postoperative mitomycin C eye drops in pterygium surgery. *Acta Ophthalmol Scand* 1999; **77:** 147–50.
6. Amano S, *et al.* Comparative study of intraoperative mitomycin C and β irradiation in pterygium surgery. *Br J Ophthalmol* 2000; **84:** 618–21.
7. Şimşek T, *et al.* Comparative efficacy of β-irradiation and mitomycin-C in primary and recurrent pterygium. *Eur J Ophthalmol* 2001; **11:** 126–32.

Preparations

USP 31: Mitomycin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Asomutan; Crisofimina; Datisan†; Maximiton; Mitocyna; Mitokebir; Mitonovag; Mitotie; Oncotaxina†; Sintemicina; Vetio; ***Braz.:*** Mitocin; ***Canad.:*** Mutamycin; ***Chile:*** Metomit†; ***Fin.:*** Mitostat; Mutamycin; ***Fr.:*** Ametycine; ***Ger.:*** Ametycine; Mitem; Mito-extra; Mito-medac; ***India:*** Mitocin; ***Mex.:*** Ifamit†; Mitocin-C; Mitolem; Mitotie; Mixandex; ***Norw.:*** Mutamycin; ***Philipp.:*** Mytoxid; ***Swed.:*** Mutamycin; ***Switz.:*** Mutamycine†; ***USA:*** Mitozytrex; Mutamycin.

Mitotane *(USAN, rINN)*

CB-313; *o,p'*DDD; Mitotaani; Mitotan; Mitotano; Mitotanum; NSC-38721; WR-13045. 1,1-Dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane.

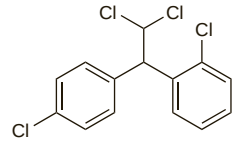
Митотан

$C_{14}H_{10}Cl_4$ = 320.0.

CAS — 53-19-0.

ATC — L01XX23.

ATC Vet — QL01XX23.



Pharmacopoeias. In *US.*

USP 31 (Mitotane). A white crystalline powder with a slight aromatic odour. M.p. is between 75° and 81°. Practically insoluble in water; soluble in alcohol, in ether, in petroleum spirit, and in fixed oils and fats. Store in airtight containers. Protect from light.

Adverse Effects

Almost all patients given mitotane have anorexia, nausea and vomiting, and sometimes diarrhoea, and about 40% suffer some central toxicity with dizziness, vertigo, sedation, lethargy, and depression. Permanent brain damage may develop with prolonged dosage. Bleeding time may be prolonged. Other common adverse effects include leucopenia, thrombocytopenia, anaemia, hypercholesterolaemia, hypertriglyceridaemia, mucositis, gynaecomastia, and headache. Ocular adverse effects may occur including blurred vision, diplopia, lenticular opacities, and retinopathy. Other adverse effects include hypersensitivity reactions, haematuria, albuminuria, skin rashes, fever, myalgia, haemorrhagic cystitis, flushing, hypertension, and orthostatic hypotension.

Precautions

Mitotane inhibits the adrenal cortex and adrenocortical insufficiency may develop during treatment; corticosteroid therapy is often required. In trauma, infection, or shock the drug should be temporarily withdrawn and corticosteroids should be given systemically. Mitotane should be given with care to patients with renal or hepatic impairment. Before mitotane therapy is begun, all possible tumour tissue from large metastases should be surgically removed, in order to minimise possible infarction or haemorrhage in the tumour. Patients should not drive or operate machinery. Behavioural and neurological assessments should be carried out regularly in patients who have been receiving treatment for 2 years or more. Plasma concentrations should be monitored to guide dosage; the therapeutic window lies between 14 and 20 micrograms/mL (see also Therapeutic Drug Monitoring, below).

Interactions

Mitotane may induce hepatic microsomal enzymes and enhance the metabolism of some other drugs, including coumarin anticoagulants.

Spironolactone. Mitotane in a dose of up to 3 g daily in a 65-year-old patient with Cushing's syndrome appeared to be ineffective and did not produce the usual adverse effects associated with mitotane while the patient was also receiving spironolactone.[1]

1. Wortsman J, Soler NG. Mitotane: spironolactone antagonism in Cushing's syndrome. *JAMA* 1977; **238:** 2527.

Pharmacokinetics

Up to 40% of a dose of mitotane is absorbed from the gastrointestinal tract; absorption increases with food. After daily doses of 5 to 15 g, concentrations in the blood of 7 to 90 micrograms/mL of unchanged drug and 29 to 54 micrograms/mL of metabolite have been reported. Mitotane has been detected in the blood for about 6 to 9 weeks after stopping treatment. It is widely distributed and appears to be stored mainly in fatty tissues. It is metabolised in the liver and other tissues and excreted as metabolites in urine and bile. From 10 to 25% of a dose has been recovered in the urine as a water-soluble metabolite.

Therapeutic drug monitoring. Monitoring of mitotane and its major metabolite *o,p'*-DDE in 2 patients receiving mitotane in low doses for Cushing's disease demonstrated that there is a prolonged lag time in the plasma concentration changes in response to alterations in dosage,[1] presumably because of the lipophilicity of both compounds which leads to accumulation in adipose tissue. A study[2] in adrenal carcinoma found that mitotane is preferentially distributed into the very-low-density lipoprotein (VLDL) fraction of the serum of patients with hypertriglyceridaemia, whereas under normolipidaemic conditions, it is bound to high-density lipoproteins and albumin. Because VLDL is not incorporated into the human adrenal cells, mitotane's lipophilicity has implications for treatment and monitoring in patients with hypertriglyceridaemia. In some studies[3,4] tumour responses were seen only in those patients achieving a serum concentration of mitotane above 14 micrograms/mL, and a small prospective study[5] found that therapeutic concentrations (defined as between 14 and 20 micrograms/mL) could be reached by sustained low doses (1 to 3 g daily), thus limiting side-effects.

1. Benecke R, *et al.* Plasma level monitoring of mitotane (o,p'-DDD) and its metabolite (o,p'-DDE) during long-term treatment of Cushing's disease with low doses. *Eur J Clin Pharmacol* 1991; **41:** 259–61.
2. Gebhardt DOE, *et al.* The distribution of *o,p'*-DDD (mitotane) among serum lipoproteins in normo- and hypertriglyceridemia. *Cancer Chemother Pharmacol* 1992; **29:** 331–4.
3. Haak HR, *et al.* Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. *Br J Cancer* 1994; **69:** 947–51.
4. Baudin E, *et al.* Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p'DDD) levels on the treatment of patients with adrenocortical carcinoma. *Cancer* 2001; **92:** 1385–92.
5. Terzolo M, *et al.* Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. *J Clin Endocrinol Metab* 2000; **85:** 2234–8.

Uses and Administration

Mitotane is an antineoplastic with a selective inhibitory action on adrenal cortex activity. It may also modify peripheral steroid metabolism. It is given in the treatment of inoperable adrenocortical tumours and has also been used in patients with Cushing's syndrome (p.2344). Dosing schedules vary. In the UK, mitotane is started at a dose of 2 to 3 g daily in patients with adrenocortical tumours, given orally in 2 or 3 divided doses, and preferably with meals. Doses may be reduced to 1 to 2 g daily after 2 months of treatment, or until a cumulative dose of 200 g, or in event of toxicity. If plasma monitoring is available, initial doses may be as high as 4 to 6 g daily in divided doses until a cumulative dose of 75 g is reached (over about 15 days). Children or adolescents may be given starting doses of 1.5 to 3.5 g/m^2 daily, in 2 or 3 divided doses, with meals; this is reduced after 2 to 3 months according to mitotane plasma concentrations. In the USA, the usual initial oral dosage is 2 to 6 g daily in 3 or 4 divided doses. Doses are usually increased to 9 to 10 g daily, unless adverse effects necessitate dose reduction. The maximum tolerated dose ranges from about 2 to 16 g daily. In some countries, mitotane may also be started at 9 to 10 g daily in 3 or 4 divided doses.

◊ A retrospective study involving 105 patients with adrenocortical carcinoma found the prognosis to be generally poor with a 5-year survival of 22% among 88 patients followed up.[1] Surgical resection was the treatment of choice; mitotane treatment had no effect on survival although 8 patients had transient tumour regression and it was of some benefit in controlling adrenal hypersecretion. However, others have previously reported improved survival in patients with adrenocortical carcinoma in whom mitotane serum concentrations were above 14 micrograms/mL, and some[2] have suggested that the poor results with mitotane in the retrospective study may have been due to low serum-mitotane concentrations (see Therapeutic Drug Monitoring, above). A further study[3] found mitotane to be of benefit only in patients with adrenocortical carcinoma undergoing palliative surgery, but of no additional benefit as an adjuvant therapy for survival amongst patients receiving curative surgical resection. However, a retrospective analysis[4] of adjuvant mitotane therapy after radical resection found that it significantly prolonged recurrence-free survival. A review[5] concluded that, although mitotane is recommended for patients with unresectable tumours, only about 35% of such tumours respond.

1. Luton J-P, *et al.* Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med* 1990; **322:** 1195–1201.
2. Haak HR, *et al.* Mitotane therapy of adrenocortical carcinoma. *N Engl J Med* 1990; **323:** 758.
3. Icard P, *et al.* Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg* 2001; **25:** 891–7.
4. Terzolo M, *et al.* Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007; **356:** 2372–80.
5. Wooten MD, King DK. Adrenal cortical carcinoma: epidemiology and treatment with mitotane and a review of the literature. *Cancer* 1993; **72:** 3145–55.

Preparations

USP 31: Mitotane Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Lisodren; ***Canad.:*** Lysodren; ***Cz.:*** Lysodren; ***Denm.:*** Lysodren; ***Fin.:*** Lysodren; ***Fr.:*** Lysodren; ***Ger.:*** Lysodren; ***Gr.:*** Lysodren; ***Hong Kong:*** Lysodren; ***Neth.:*** Lysodren; ***Pol.:*** Lysodren; ***Spain:*** Lysodren; ***UK:*** Lysodren; ***USA:*** Lysodren.

Mitoxantrone Hydrochloride

(BANM, USAN, rINNM)

CL-232315; DHAD; Dihydroxyanthracenedione Dihydrochloride; Hidrocloruro de mitoxantrona; Mitoksantron Hidroklorür; Mitoksantronihydrokloridi; Mitoksantrono hidrochloridas; Mitoxantron dihydrochlorid; Mitoxantrone, chlorhydrate de; Mitoxantron-hidroklorid; Mitoxantronhydroklorid; Mitoxantroni Dihydrochloridum; Mitoxantroni hydrochloridum; Mitozantron Hidroklorür; Mitozantrone Hydrochloride; NSC-301739. 1,4-Dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino]anthraquinone dihydrochloride.

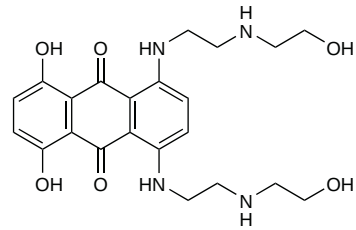
Митоксантрона Гидрохлорид

$C_{22}H_{28}N_4O_6,2HCl$ = 517.4.

CAS — 65271-80-9 (mitoxantrone); 70476-82-3 (mitoxantrone hydrochloride).

ATC — L01DB07.

ATC Vet — QL01DB07.



(mitoxantrone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Mitoxantrone Hydrochloride). A dark-blue, electrostatic, hygroscopic powder. Sparingly soluble in water; practically insoluble in acetone; slightly soluble in methyl alcohol. Store in airtight containers.
USP 31 (Mitoxantrone Hydrochloride). A dark-blue powder. Sparingly soluble in water; practically insoluble in acetone, in acetonitrile, and in chloroform; slightly soluble in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712. Mitoxantrone is reported to be better tolerated than doxorubicin. The nadir of the white cell count usually occurs about 10 days after a dose, with recovery by day 21. Elevation in liver enzyme values may occur; there are occasional reports of severe hepatic impairment in patients with leukaemia, in whom doses are generally higher and adverse effects of mitoxantrone may be more frequent and severe.

Transient blue-green coloration of the urine, and occasionally the sclerae, may occur. Tissue necrosis is rare after extravasation.

Severe neurotoxicity has resulted from erroneous intrathecal dosage; local or regional neuropathy has followed intra-arterial injection. Care is required in patients with pre-existing heart disease, or who have had prior anthracycline treatment or radiotherapy to the chest, as they are at increased risk of cardiotoxicity; regular cardiac examinations should be performed in such patients and in those who receive a total cumulative dose of mitoxantrone in excess of 160 mg/m^2. Care is also required in patients with hepatic impairment. Regular blood counts should be performed during treatment.

Alopecia. Two patients receiving therapy with mitoxantrone developed selective alopecia of white but not of dark hair.[1]

1. Arlin ZA, *et al.* Selective alopecia with mitoxantrone. *N Engl J Med* 1984; **310:** 1464.

Breast feeding. Mitoxantrone was detected in the breast milk of a woman with acute promyelocytic leukaemia in remission who was given consolidation chemotherapy that included mitoxantrone 6 mg/m^2 on days 1 to 3. Concentrations were 120 nanograms/mL just after the third dose and 18 nanograms/mL 28 days after treatment. Although she breast fed her neonate from 3 weeks after the completion of the course of treatment and no adverse effects were seen, the authors recommended that women treated with mitoxantrone should not breast feed.[1]

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; **48:** 131–2.

Effects on the heart. Data from over 4000 patients treated with mitoxantrone included 172 reports of cardiac events, including 42 cases of congestive heart failure and 66 of decreased ejection fraction.[1] Previous anthracycline therapy increased the risk, and congestive heart failure seemed to be more likely in patients exposed to a cumulative mitoxantrone dose of 160 mg/m^2, or 100 mg/m^2 in those already given anthracyclines. In a further 78 patients,[2] clinical heart failure developed in 2 after cumulative doses of 174 and 243 mg/m^2. Four of 9 other patients given mitoxantrone in doses above 100 mg/m^2 showed signs of cardiotoxicity, and a further patient previously given doxorubicin 313 mg/m^2 had a fall in stress ejection fraction after only 47 mg/m^2 of mitoxantrone. However, sinus bradycardia has also been reported[3] in 2 previously untreated patients after starting continuous infusions of mitoxantrone 10 mg/m^2. For information on the cardiotoxicity of anthracyclines, to which mitoxantrone is structurally related, see under Adverse Effects and Treatment of Doxorubicin, p.713.

1. Crossley RJ. Clinical safety and tolerance of mitoxantrone. *Semin Oncol* 1984; **11:** (suppl 1): 54–8.
2. Stuart-Harris R, *et al.* Cardiotoxicity associated with mitoxantrone. *Lancet* 1984; **ii:** 219–20.
3. Benekli M, *et al.* Mitoxantrone-induced bradycardia. *Ann Intern Med* 1997; **126:** 409.

Handling and disposal. *Urine and faeces* produced for up to 7 days after a dose of mitoxantrone should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hypersensitivity. In a report of 3 patients, allergic-type reactions to mitoxantrone included vasculitis, facial oedema and skin rashes, and in one, breathlessness, tachypnoea, cyanosis, and unrecordable pulse and blood pressure.[1] Allergic reactions to the drug appear to be rare.

1. Taylor WB, *et al.* Allergic reactions to mitoxantrone. *Lancet* 1986; **i:** 1439.

Interactions

For a report of the effect of ciclosporin in patients receiving mitoxantrone and etoposide, see p.719.

Pharmacokinetics

After intravenous doses mitoxantrone is rapidly and extensively distributed to body tissues, and slowly excreted in urine and bile as unchanged drug and metabolites. The elimination half-life is reported to range from 5 to 18 days. Between 6 and 11% of a dose has been recovered from urine, and 13 to 25% in faeces, within 5 days. It does not appear to cross the blood-brain barrier, but it is distributed into breast milk.

◊ References.

1. Ehninger G, *et al.* Pharmacokinetics and metabolism of mitoxantrone: a review. *Clin Pharmacokinet* 1990; **18:** 365–80.

Uses and Administration

Mitoxantrone is an antineoplastic structurally related to doxorubicin (p.712). Its mode of action has not been fully established but it inhibits topoisomerase II and causes DNA strand breakage, as well as intercalating with DNA. It is cell-cycle non-specific but is most active against cells in the late S phase.

It is used in the treatment of metastatic breast cancer (p.661), and of non-Hodgkin's lymphomas (p.656), alone or with other agents. It may also be given to treat adult acute myeloid leukaemias (p.652). Mitoxantrone has also been used in patients with hormone-refractory prostate cancer (p.671), liver cancer (p.667), and ovarian cancer (p.670).

In addition, mitoxantrone is used in the management of secondary progressive or relapsing multiple sclerosis (see below), to reduce neurological disability or the frequency of relapses.

Mitoxantrone is given as the hydrochloride, but doses are expressed in terms of the base; 1.2 mg of the hydrochloride is equivalent to about 1 mg of mitoxantrone. In the treatment of breast cancer, prostate cancer, liver cancer, and lymphomas, a dose equivalent to mitoxantrone 14 mg/m^2 is given initially, then repeated every 3 weeks. It is diluted to at least 50 mL in sodium chloride 0.9% or glucose 5% and injected over at least 3 minutes into a freely-running intravenous infusion of either. Subsequent doses may be adjusted according to the degree of myelosuppression produced. Initial dosage may need to be reduced to 12 mg/m^2 in debilitated patients or those who have had previous chemotherapy. Doses should also probably be reduced when mitoxantrone is given as part of a combination regimen: an initial dose of 10 to 12 mg/m^2 has been suggested.

In the treatment of patients with acute myeloid leukaemia a dose of 12 mg/m^2 daily for 5 days may be given to induce remission; alternatively a similar dose may be given for 3 days with cytarabine.

Cardiac examinations are recommended in all patients who receive a cumulative dose of mitoxantrone greater than 160 mg/m^2; left ventricular ejection fraction (LVEF) should be determined before each dose in patients who have received a cumulative dose in excess of 100 mg/m^2. Regular blood counts should be per-