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Review paper

Mitoxantrone: Bluebeard for malignancies

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Mitoxantrone, an anthracenedione derivative, has been used for preclinical and clinical studies from the end of the 1970s. Several working mechanisms are suggested such as intercalation and electrostatic interactions with DNA with or without involvement of topoisomerase II, immunosuppressive effects and inhibition of prostacyclin synthesis. Efficacy of mitoxantrone alone or in combination with other chemotherapeutic drugs has been especially demonstrated in patients with breast cancer, leukemia and lymphoma. Locoregional (but not intrathecal) therapy with this drug is possible because it is not a vesicant. It has an improved tolerability profile compared with doxorubicin. Dose-limiting toxicity is myelotoxicity and mucositis. Therefore this drug has recently also been used in high doses with bone marrow support and in combination with hematopoietic growth factors. Cardiotoxicity is less frequent than after doxorubicin and daunorubicin. However, cardiac function tests are warranted after cumulative doses >160 mg/m^2 or earlier if additional risk factors, namely previous mediastinal irradiation, anthracycline therapy or cardiovascular disease, are present.

Key words: Mitoxantrone.

Introduction

Anthracyclines, such as doxorubicin and daunorubicin, are highly effective chemotherapeutic drugs. Intensive research is performed to find drugs with the same or higher activity but less side-effects. Pronounced side-effects are cardiomyopathy, nausea, vomiting and alopecia. In the 1970s the anthracenedione derivative mitoxantrone (1,4-dihydroxy - 5,8 - bis[2 - (2 - hydroxyethylamino)ethyl amino]-9,10-anthracenedione dihydrochloride) (Novantrone, Lederle Laboratories, Pearl River, New York), was synthesized (Figure 1). This blue compound lacks the amino sugar moiety and tetracycline A ring of the anthracyclines (Figure 2)

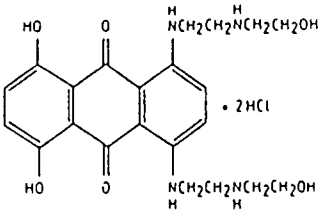

Figure 1 Structure of mitoxantrone.

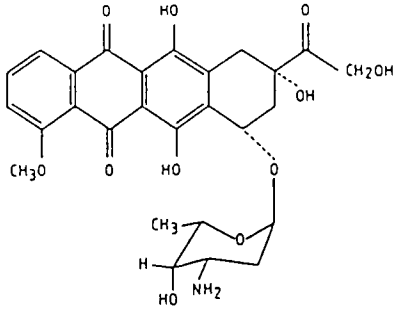

Figure 2 Structure of doxorubicin.

and it has a molecular weight of 517.4. In 1979, phase I clinical trials started. By now mitoxantrone has obtained, after numerous clinical studies, a role in the treatment of a number of tumors. Apart from a huge number of articles, several reviews about mitoxantrone have appeared.[1–7] This review will pay special attention to results obtained over the last few years using mitoxantrone.

Mechanism of action

As for the anthracyclines, the exact working mechanism of mitoxantrone has not been clarified

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yet and based on *in vitro* work its actions are found to be multiple. Thus far, targets at the nuclear level are the most likely.[8–14] Different types of DNA damage can be detected *in vitro* after incubation with mitoxantrone. This damage may result from the intercalation and/or electrostatic binding of mitoxantrone with DNA with or without the involvement of cellular enzymes such as topoisomerase II. DNA intercalation can also be responsible for a decrease of ^{3}H-thymidine and ^{3}H-uridine incorporation, DNA conformational changes and nuclear alterations. The other possible mechanisms of action of anthracyclines have not been described for mitoxantrone yet. In particular, free radical formation could not be detected. This might be an explanation of the less marked mitoxantrone-induced cardiotoxicity *in vivo* compared with doxorubicin.[7,15]

Although mitoxantrone blocks the cell cycle in G2, its toxicity is not cycle specific.[9,16] It has been suggested that there can be synergy between mitoxantrone and Ara-C, and mitoxantrone and hyperthermia.[17,18] The activity of mitoxantrone can be enhanced by cells sensitive for hormonal stimulation.[19]

Other effects of mitoxantrone are immunosuppressive effects and inhibition of prostaglandin synthesis.[20–22]

Which of the *in vitro* working mechanisms especially play a role in anti-tumor activity *in vivo* is not yet completely clear.

Resistance

The effect of most chemotherapeutic drugs is influenced by the presence of intrinsic, or the development of acquired, resistance for the drug. A number of mechanisms are held responsible for anthracycline resistance, such as the presence of the P-glycoprotein-mediated efflux pump, altered intracellular drug distribution, altered DNA damage by change of enzymes such as topoisomerase II and increased cellular drug detoxification. Together with resistance for anthracyclines there is often cross-resistance with epipodophyllotoxins and vinca alkaloids. In cell lines made resistant for anthracyclines cross-resistance to mitoxantrone can exist, although often to a lesser degree.[23–26]

In the P-glycoprotein-positive doxorubicin-resistant sublines of the NCI-H69 human small cell lung cancer cell line and the EMT6 murine mammary tumor cell line with some cross-resistance for mitoxantrone, verapamil and cyclosporin A were efficient modifiers of mitoxantrone resistance.[27] In the doxorubicin-resistant P-glycoprotein-negative subline, GLC_4-ADR, of the human small cell lung cancer cell line GLC_4, cross-resistance for mitoxantrone was observed as well as a decreased topoisomerase II compared with the sensitive line.[28]

There are indications that tumor cells in which vincristine or VP-16 resistance has been induced generally express full or partial cross-resistance to doxorubicin and mitoxantrone.[29] In CEM/VM-1, a human leukemic cell line, atypical multiple drug resistance is observed: despite resistance and cross-resistance to VP-16, anthracyclines, mAMSA and mitoxantrone, these cells remain sensitive to vinca alkaloids.[30]

There are, however, also studies in which the cell line is made specifically resistant for mitoxantrone. A human colon carcinoma cell line, WiDr, was made resistant for mitoxantrone (21-fold).[31,32] There was cross-resistance, although to a lesser degree for doxorubicin (eight-fold) and vinblastine (two-fold). There was some enhanced efflux of mitoxantrone in the resistant line, but P-glycoprotein was negative and verapamil did not influence mitoxantrone accumulation and retention in the resistant cells. In another study, two sublines of the breast carcinoma cell line MCF_7 were obtained.[25] One was made resistant *in vitro* for mitoxantrone and one for doxorubicin. Only the doxorubicin-resistant line was P-glycoprotein positive. Both lines showed an enhanced drug efflux. Harker *et al.* described a mitoxantrone-resistant leukemia cell line which lacked P-glycoprotein and had no cross-resistance to vinca alkaloids.[33] A human gastric carcinoma cell line was made resistant for mitoxantrone. No overexpression of P-glycoprotein was found. In the resistant line membrane vesicles were formed and vesicular drug binding and drug compartmentalization were found.[34] An especially striking result of these studies is the fact that mitoxantrone did not clearly induce P-glycoprotein-mediated drug efflux.

In conclusion, the mechanisms of mitoxantrone resistance *in vitro* are only partially elucidated. A topoisomerase II mediated resistance, different drug compartmentalization and an increase in non-P-glycoprotein drug efflux are possible explanations. Doxorubicin-resistant P-glycoprotein-positive cells can be cross-resistant for mitoxantrone, but mitoxantrone-resistant tumor cells do not have to be P-glycoprotein positive.

In the clinic, cross-over studies showed that there is no complete cross-resistance between mitoxantrone and doxorubicin.[35,36]

Pharmacokinetics

The pharmacokinetics of mitoxantrone were extensively studied in animals and patients after iv and locoregional treatment and were recently summarized in a review by Ehninger *et al.*[7] Mitoxantrone has been measured with a variety of assays of which the HPLC assay now appears to be the most sensitive. Instability of the drug, binding of the drug to proteins, plastics and glassware, and a high variability in the clinical condition of the patients may be reasons for varying results obtained in these studies. Most investigators did not measure metabolites of mitoxantrone. After intravenous administration, a biphasic as well as a triphasic pattern of plasma mitoxantrone disappearance has been described. Most studies consider as the best-fitting model the triphasic pattern with varying half-lives reported in the literature: for the α half-life 4.1–10.7 min, the β half-life 0.3–3.1 h and the γ half-life 10 h–12 days.[7,37–40] The drug has a high protein binding (e.g. plasma protein binding of 78%), and it binds extensively to blood cells and body tissues. It has a very large volume of distribution of 1875–2248 l/m^2,[39,41] although lower volumes of distribution have also been reported.[37,40] Van Belle *et al.* found a lower apparent volume of the central compartment of patients who received mitoxantrone in combination with methotrexate and vincristine.[42] Mitoxantrone can be detected in leukocytes until 14 days after the infusion.[43] In tissues obtained at autopsy from patients who died 10–272 days after their last mitoxantrone course (6–16 mg/m^2/course, total dose 6–100 mg/m^2), mitoxantrone was detectable in tissues from all patients, with highest concentrations in liver, pancreas, thyroid, spleen and heart, and the lowest concentrations in the brain.[44] In this postmortem study tumor tissue generally contained less mitoxantrone than surrounding normal tissues. In a patient treated with iv mitoxantrone 12 mg/m^2, the concentration of mitoxantrone in the pleura was six-fold higher than in the plasma at 72 h.[42] In 10 patients with intracerebral tumors mitoxantrone was administered before surgery (0.2–25.8 h). In all patients but one, mitoxantrone concentration in the tumor was higher than in plasma.[45]

The drug is mainly excreted in the bile with only about 10% excretion in the urine.[46] In patients with hepatic dysfunction a reduction of total drug clearance was observed.[47] In breast cancer patients with elevated bilirubin a tendency to more hematologic toxicity was observed, whereas no difference in toxicity was observed between patients with normal and elevated bilirubin and hepatocellular carcinoma.[48,49]

The pharmacokinetic properties of the drug during continuous infusion and the various locoregional routes of administration are described in 'Routes of administration'.

Routes of administration

Intravenous (iv); bolus normal dose, continuous infusion and high-dose

One of the first phase I trials with mitoxantrone studied the effect of weekly iv mitoxantrone. Dose-limiting leukocytopenia was seen at 4–5 mg/m^2.[50] The most frequently studied schedule for mitoxantrone administration in solid tumors is a single dose, repeated every three to four weeks or daily for five days every four weeks. For the single bolus the maximally tolerated dose was 12–14 mg/m^2.[51] For the daily × 5 schedule in leukemias the maximally tolerated dose was considered to be 4–12 mg/m^2/day. The dose-limiting factor was mainly leukocytopenia with mucositis at higher dosages.[52,53]

There are also reports about mitoxantrone as continuous infusion. Anderson *et al.*[54] showed in a phase I trial comparable toxicity of a 24 h continuous iv infusion and iv bolus administration. For 3 weeks of continuous infusion, using a venous access port with portable pump, a dose of 1.1 mg/m^2/day was recommended by Greidanus *et al.*[43] after a phase I study. Grade 3 leukocytopenia was the dose-limiting factor at 1.3 mg/m^2/day for 3 weeks. Plasma steady state was reached after 35 h. There was a linear relationship between dose administered and mitoxantrone level in plasma. During the whole infusion period the mitoxantrone level in leukocytes increased. The area under the curve in leukocytes was higher with continuous infusion of 1.1 mg/m^2/day for 21 days compared with bolus injection of 12 mg/m^2. Thus, continuous infusion may be a way to increase intracellular drug uptake. Kaminer *et al.* also treated patients with relapsed acute nonlymphocytic leukemia (ANLL) with 12 mg/m^2 daily as continuous infusion for 5 days.[55] Toxicity included myelosuppression, mucositis and hepatic dysfunction.

Mitoxantrone is an interesting drug for dose escalation. *In vitro*, in the human tumor colony forming assay, there is a dose–response relationship for mitoxantrone. It has activity in patients with breast cancer, lymphoma, leukemia and ovarian

cancer. All these tumor types are considered to be interesting tumors for treatment with drug dose escalation or even high-dose chemotherapy and autologous or allogenic bone marrow transplantation. In the recent studies of Ten Bokkel Huinink *et al.* with mitoxantrone and of Ho *et al.* with mitoxantrone plus high-dose Ara-C, the addition of GM-CSF showed promising results to underscore the opportunity to treat patients with escalating doses of mitoxantrone and hematopoietic growth factors without bone marrow support.[56,57]

There are no studies available with mitoxantrone as single agent and bone marrow re-infusion. The prolonged terminal half-life of mitoxantrone and intensive but reversible tissue binding of the drug is of some concern in designing the moment of bone marrow re-infusion. Our group conducted a phase I trial with cyclophosphamide or melphalan and escalating doses of mitoxantrone in solid tumors.[58] The first eight patients received 7 g/m^2 cyclophosphamide and mitoxantrone 30, 45 or 60 mg/m^2, both iv and divided over 3 days. Bone marrow was reinfused on day 7. Four out of these eight patients developed for unknown reasons hemorrhagic cystitis despite adequate precautions. For this reason, at the 60 mg/m^2 mitoxantrone dose, instead of cyclophosphamide, melphalan 180 mg/m^2 was added. Dose-limiting toxicity was mucositis at 75 mg/m^2 mitoxantrone plus melphalan. For phase II studies 60 mg/m^2 mitoxantrone with 180 mg/m^2 melphalan was proposed. During mitoxantrone no arrhythmias or signs of heart failure were observed. Two out of eight evaluable patients showed modest reduction in radionucleotide ejection fraction. The relatively long bone marrow recovery time found in this study for the combination of mitoxantrone and melphalan may be explained by the earlier mentioned pharmacological properties of the drug. In further studies, the hematopoietic growth factors may facilitate the use of high-dose mitoxantrone in the bone marrow transplant setting.

Preliminary data are available from a study with mitoxantrone 30 mg/m^2/day 1 and etoposide 1.200 mg/m^2 and thiotepa 750 mg/m^2, the last two drugs divided over three days, with autologous bone marrow support. Thirty-two pretreated women with metastatic breast cancer were entered in the study and 13 of them received two courses. Of the 28 evaluable patients 25% experienced a complete remission and 54% a partial remission. There were three early deaths. Main reported toxicity consisted of mucositis (69%, grade 3–4) and infections.[59] Shortly, more data will be available as there are a number of studies in progress with combination regimens comprising mitoxantrone and hematopoietic stem cell support.

Intraperitoneal (ipt)

Three characteristics of mitoxantrone make it interesting to study this drug for ipt administration. Firstly, mitoxantrone is, in contrast to doxorubicin, not a vesicant[60]. Secondly, mitoxantrone is metabolized by the liver, reducing systemic exposure following ipt administration.[61] Thirdly, after intravenous administration long-lasting tissue levels of mitoxantrone are found, suggesting that mitoxantrone may remain localized to the peritoneal cavity when given ipt.[39,44]

Alberts *et al.*[62] studied in a phase I trial the effect of ipt mitoxantrone, 12–38 mg/m^2 ipt every four weeks, on residual or recurrent ovarian ($n = 31$) and colon ($n = 2$) cancers. Exact information on ipt dwell time in individual patients of the drug was not reported. Response was observed in five out of 17 evaluable patients. Although leukopenia was observed, especially in the highest dose, chemical peritonitis was dose-limiting toxicity. A dose of 23 mg/m^2 every three to four weeks was advised for phase II studies. Pharmacokinetic analysis showed an increased exposure of the peritoneal cavity compared to the systemic circulation. In a phase II trial Markman *et al.*[63] entered 31 patients with refractory ovarian cancer. Initially, per cycle 30 mg/m^2 mitoxantrone was administered ipt. Because of local abdominal pain this had to be reduced to 20 mg/m^2. Also at this dose 74% of the patients needed narcotic analgesia. In the group with small volume disease a remission rate of 33% was achieved. Seven of 21 patients previously treated with ipt cisplatin responded, including four patients who previously failed to respond to ipt cisplatin.

Intrapleural (ipl)

Mitoxantrone was given ipl to eight patients with metastatic breast cancer and recurrent malignant pleural effusion.[64] After pleural drainage, 30 mg mitoxantrone was administered ipl once or twice and was left ipl for 48 h. Neither local nor systemic side-effects were observed. Good clinical response to ipl mitoxantrone (sometimes administered with 5-FU, tetracycline–HCl and fibrin glue) was documented, with reduction in frequency of pleurocenteses in four of them and without

recurrence for 6 months under subsequent chemotherapy in the other four patients.

Intrathecal (it)

Three case reports of patients with acute leukemia with CNS localization were described.[65–67] In all patients blasts in CSF disappeared after treatment with mitoxantrone it, even when they were pretreated with methotrexate and Ara-C it. However, paraplegia occurred in two patients which was most probably related to the administration of mitoxantrone it. In a study in monkeys neurotoxicity of it mitoxantrone was noted as well.[68] In mice and rats injection of doxorubicin and mitoxantrone caused a similar dose-dependent early and delayed neurotoxicity.[69] Because of these serious side-effects further trials with mitoxantrone it were precluded.[68,70]

Intraarterial (ia)

Intraarterial mitoxantrone was given in several studies.[71,72] Hepatic arterial infusion with mitoxantrone for hepatocellular carcinoma was given analogously to previous treatment of this tumor with anthracyclines and resulted, in the study of Shepherd *et al.*, in a response rate of 27%.[71] Complication of thrombosis and dissection were present but asymptomatic. De Dycker *et al.*[72] used locoregional treatment of mitoxantrone in the lateral thoracic artery and in the internal mammary artery successfully in patients with primary locally advanced breast cancer. After treatment 18 of 20 tumors had become operable and in seven patients more than 50% tumor regression was achieved. Side-effects due to this special mode of administration were reduced compared with iv treatment.

Intravesical (ivs)

In a phase I study for recurrent superficial bladder tumors, mitoxantrone was instilled in the bladder and left *in situ* for 2 h once weekly during six weeks.[73] Dysuria, hematuria and urinary frequency were dose limiting at 10–10.5 mg. One patient treated with 7.5 mg mitoxantrone had bladder contracture. One patient reached CR, others (11/27) had an increase in the interval free of recurrence. Systemic absorption was negligible and systemic toxicity was not observed.

Intratumoral (itu)

In two patients the efficacy of itu mitoxantrone, after local application in inoperable, recurrent esophageal carcinoma, was studied.[74] Twenty mg of mitoxantrone was administered without local or systemic side effects. A transient response was observed in both patients.

Efficacy in the treatment of solid tumors

Before the spectrum of indications for mitoxantrone became clear, numerous phase I and II studies had been performed. The summaries of the initial studies were described in a number of reviews.[16]

Mitoxantrone has shown limited activity in many advanced solid tumors. In patients with lung cancer, both small cell and non-small-cell, the overall response was less than 1%.[75–78] Most patients had received prior chemotherapy. The few responses were observed in pretreated as well as in untreated patients.

In cervical cancer the overall response was again below 1%.[79–82] Toxicity was comparable with that of studies with mitoxantrone for other solid tumors. Also, in patients with advanced carcinoma of the vulva or vagina and advanced or recurrent endometrial carcinoma, no antitumor activity of mitoxantrone was observed.[83–85]

In advanced or metastatic sarcomas hardly any response after mitoxantrone was noticed, even when patients were not pretreated with chemotherapy.[86–88] At the moment there is also no indication for treatment with systemic mitoxantrone in melanoma, advanced renal and bladder carcinoma, stomach and pancreatic carcinoma, head and neck cancer, mesothelioma and Kaposi's sarcoma.[89–98]

In patients with primary liver cancer treated with one iv dose of single-agent mitoxantrone every three weeks, the overall response was 8%.[99–104] In particular, the results of the latest studies with intravenous mitoxantrone were disappointing. Apart from low response rate, the toxicity, especially hematologic and cardiac, was not negligible. The response percentage (27%) after intraarterial mitoxantrone for hepatocellular carcinoma seemed better, although these results have not yet been confirmed.[71]

Single-agent mitoxantrone was also administered in patients with advanced pediatric malignant solid tumors, with exception of brain tumors and

lymphomas.[105] One complete and two partial responses were observed in 26 patients with rhabdomyosarcoma and one of 22 patients with neuroblastoma also had a partial response. The four patients who responded to mitoxantrone had all been pretreated with doxorubicin. These disappointing results can probably partly be explained by the fact that the studies are often performed in heavily pretreated patients.

In a number of tumor types mitoxantrone is a very active drug. Results obtained in breast carcinoma, ovarian carcinoma and hematologic malignancies do deserve special attention.

Mitoxantrone in breast carcinoma

Of all solid cancers, breast cancer is the best indication for treatment with mitoxantrone. The response to mitoxantrone depends on the number of prior therapies. Patients who have not been treated or have received only adjuvant chemotherapy have a response rate of about 30–36%[106–110] when treated with 12–14 mg/m^2 mitoxantrone as single agent in a 3-week schedule. Only Wilson and Paterson[111] found a far lower response rate, of 13%, probably partly because of dose reduction. In heavily pretreated patients, including both doxorubicin and mitoxantrone pretreatment, response was absent even with dosages up to 25 mg/m^2 every 3–4 weeks.[112] Some dose intensification did not improve the response rate when compared with response rates reported for less myelotoxic regimens.[113] Harris *et al.* compared short-term (four) courses of bolus mitoxantrone with long-term chemotherapy.[110] There was no difference in response duration, disease progression and survival between the two groups. Drug resistance apparently develops early during therapy, and therefore short-term treatment may be sufficient. A special study was performed in patients with liver metastases.[114] Liver metastases are associated with a poor prognosis and patients with liver dysfunction are often excluded from clinical trials. With mitoxantrone the response rate was rather disappointing (16%) and myelotoxicity was more than expected. Chlebowski *et al.*[48] studied the safety and efficacy of mitoxantrone in hyperbilirubinemic breast cancer patients. They conclude that patients with bilirubin <3.5 mg/dl can receive 14 mg/m^2 mitoxantrone with reasonable chance for benefit, and that patients with severe hepatic dysfunction and poor performance should not be given mitoxantrone, because of the myelosuppression and/or early death in this group. No definite recommendations for mitoxantrone dosage in patients with severe hyperbilirubinemia (bilirubin ≥ 3.5 mg/dl) and favorable performance status were given.

Continuous infusion of mitoxantrone during 14 days resulted in a 60% response rate. However, the number of treated patients was small and the number of side-effects, especially thrombosis of the axillary vein due to venous access port and pulmonary embolism, was high.[115]

Recently, four studies were published in which randomized cross-over treatment between mitoxantrone and doxorubicin was performed. In three of them a comparison of activity and toxicity between mitoxantrone and doxorubicin was made,[35,36,116] whereas in the fourth study[117] the primary endpoint was patient drug preference. The conclusions drawn from these studies were all comparable: despite an overall better response of doxorubicin than of mitoxantrone, when given in doses that caused equal myelotoxicity, this difference was never significant. Toxicity scores were different for frequency and severity of nausea and vomiting in all studies with a far better outcome for mitoxantrone than for doxorubicin. Also, less mucositis, stomatitis, alopecia and cardiotoxicity was observed after mitoxantrone compared with doxorubicin. The question of whether or not cross-resistance exists between mitoxantrone and doxorubicin has not been solved yet. Neidhart and colleagues found incomplete cross-resistance between mitoxantrone and doxorubicin because 15% of the patients responded to one agent after having failed to respond to the other.[35] Henderson *et al.* observed in 4% of their patients, who were previously stable or had responded to doxorubicin, a secondary response after cross-over to mitoxantrone.[36] The 11% of patients who responded secondarily to doxorubicin all had failed initially to respond to mitoxantrone. When patients were enabled to select their preference, based primarily on side-effects, 72% chose mitoxantrone, whereas 11% chose doxorubicin and 17% did not have a preference.[117]

In patients with metastatic breast cancer a comparison was made between the combination regimen with cyclophosphamide, mitoxantrone, 5-fluorouracil (CNF) and cyclophosphamide, doxorubicin, 5-fluorouracil (CAF).[118,119] No significant difference in response rate, in response duration, in overall survival, in quality of life and in hematologic toxicity was seen between the two treatment groups, but alopecia and cardiac toxicity

and the overall incidence of stomatitis and mucositis was significantly higher in the CAF treated patients than in the CNF group. In a phase II trial in which mitoxantrone and doxorubicin were combined in 25 patients with metastatic breast cancer, 52% achieved a partial response.[120] The only remarkable side-effect was cardiac toxicity with a reduction in ejection fraction in three of 15 patients in whom this was measured. However, two of the three patients had pericardial effusion, which was possibly disease related.

Mitoxantrone was given in several other combination treatments. In general, there seems to be no benefit of these combination regimens compared with single-agent mitoxantrone therapy, although combination with cyclophosphamide improved the response rate in some studies.[121,122] However, in the study of Bennett *et al.*[119] the overall response with this combination was not better. Dose reduction of chemotherapeutic drugs because of synergistic toxicity may be an explanation for the absence of improved results in other combination therapies compared with single-agent therapy with mitoxantrone in metastatic breast cancer.[123–126] Several reports have been published about the combination mitomycin C, mitoxantrone and methotrexate, with an objective remission in 50–60% of the patients. Severe myelosuppression was reported but was probably related to excessive dosages used in patients with impaired liver, renal or bone marrow function.[127–131]

In conclusion, mitoxantrone is an effective cytostatic drug in treatment of patients with advanced breast cancer. Mitoxantrone is useful both as a single agent and in combination therapy only if adequate dosage can be given. Even in case of moderate liver dysfunction, mitoxantrone can be used without untoward toxicity. Compared with doxorubicin, mitoxantrone is slightly less effective, but this difference was never statistically significant. Overall toxicity is less with mitoxantrone compared with doxorubicin. This concerns especially the difference in incidence and severity of alopecia, nausea, vomiting and also of cardiotoxicity.

Mitoxantrone in ovarian cancer

In a first-line regimen in which mitoxantrone was combined with cisplatin, a response rate of 80% was achieved.[132] In other studies mitoxantrone was used as at least a second-line regimen.[133–136] The results of these studies vary between 1% and 28% response rates with a tendency towards absence of responses in heavily pretreated patients. However, it might be possible that mitoxantrone is effective even in heavily pretreated patients when a higher dose could be used.[135,136] Markman *et al.* described a total response rate of 24% when patients with refractory ovarian cancer were treated with intraperitoneal mitoxantrone.[63] (See discussion of ipt in routes of administration.) Because of the high local toxicity this kind of administration of mitoxantrone was not recommended as a standard treatment.

Efficacy in the treatment of hematologic malignancies

Acute leukemias

About 70% of patients with ANLL who have achieved a complete remission after induction therapy will relapse. With conventional chemotherapy the remission rate after first salvage is less than 30% and in subsequent salvages even less than 10%. After relapse the long-term survival of this group is less than 5%.[137]

Mitoxantrone has been used in various different treatment schedules as single agent or in combination therapy, especially with Ara-C, in the treatment of acute leukemias. In most studies, mitoxantrone was used as second-line treatment, but treatment with mitoxantrone in untreated patients with leukemias has been performed more recently. Mitoxantrone seems to be useful in acute lymphocytic leukemia (ALL) as well as in the blastic phase of chronic myelogenous leukemia (CML-BC), but until now the most extensive evaluation has been performed for ANLL.

For the description of the role of mitoxantrone in first-line and salvage treatment, a selection has been made from the numerous publications that have appeared about this subject.

In a randomized trial in 216 previously untreated patients with ANLL who received Ara-C (100 mg/m^2/day × 7 days) with either mitoxantrone (12 mg/m^2/day × 3 days) or daunorubicin (45 mg/m^2/day × 3 days), the complete response rate was respectively 63% and 53%.[138,139] After one course 89% of the mitoxantrone-treated patients observed a response and 68% of the daunorubicin-treated patients. Patients over the age of 60 had a far worse outcome in both treatment arms than those younger than 60 years of age. In a much smaller study, four out of five previously untreated patients with ANLL achieved CR after therapy with mitoxantrone (10–12 mg/m^2/day × 5 days) combined with Ara-C (1 g/m^2 twice daily × 3 days).[140]

Mitoxantrone has been used as single agent in several studies with patients with refractory or relapsed ANLL, ALL and with CML-BC.[52,53,141–144] The most commonly used regimen consists of mitoxantrone 10–12 mg/m^2/day × 5 days. The overall response rate with this schedule varied between 20% and 48%,[53,142–144] whereas in two patients with first relapse acute promyelocytic leukemia both achieved complete remission.[141] The overall response rate of 10% in 41 patients with acute refractory leukemia treated with 4–12 mg/m^2/day × 5 days, described by Estey *et al.*, was remarkably low.[52] Prentice compared two different treatment schedules of mitoxantrone, namely 20–32 mg/m^2 as single dose or 10 mg/m^2/day × 5 days.[142] The five-day regimen was superior with a response rate of 48% compared with 21% in the single-dose group. Bezwoda *et al.*[144] reported a better response in patients with relapsed ANLL (52%) than patients with relapsed ALL (33%). The response in refractory ANLL, 24%, was worse than in patients with relapsed ANLL.

Many studies were performed with the combination treatment consisting of mitoxantrone and Ara-C.[137,140,142,145–148] Treatment schedules varied between mitoxantrone 5 mg/m^2/day × 5 days plus Ara-C 3 g/m^2 twice daily × 3 days[137,147,148] and mitoxantrone 10–12 mg/m^2/day × 3–5 days and Ara-C 1–3 g/m^2 twice daily × 3–5 days.[140,145,146] Prentice *et al.* used another regimen in which Ara-C 100 mg/m^2 was given continuously during seven days[142,149] combined with mitoxantrone 10 mg/m^2/day × 3–5 days. The overall response in the group with the lower mitoxantrone dose varied between 30% and 36% and concerned patients with refractory ANLL, refractory ALL and CML-BC. In the patients who received the higher mitoxantrone dose the overall response rate was in all studies about 60%. Most of the evaluable patients had refractory or relapsed ANLL. Paciucci *et al.*[149] reported a remarkable difference in response between ANLL patients with first relapse, 62.5% and the response of patients with primary refractory ANLL, 23%, whereas no response was observed in patients with a second relapse.

In patients with refractory ANLL and ALL, and in relapsed ALL and CML-BC, mitoxantrone in its most common dose of 10–12 mg/m^2/day × 5 days was used in combination with several other drugs such as etoposide,[150] vincristine,[151,152] daunorubicin[151] and prednisolone.[152] In the 97 evaluable patients in these studies the response rate was *circa* 55% in each regimen.

In conclusion, mitoxantrone is an effective drug in acute leukemias, both as first-line therapy and as salvage regimen. In salvage therapy especially, the response rate is higher if the drug is administered over several days, at higher doses and in combination with other chemotherapeutic drugs. In general, response seems better for patients with relapsed ANLL than with ALL, in first relapse than in second relapse and in relapsed ANLL than in refractory ANLL. In first-line therapy, based on the results of one study, a slightly but not significantly better response for mitoxantrone than for daunorubicin was found.

Malignant lymphomas

Gams *et al.*[153] conducted two separated trials with mitoxantrone as single-agent therapy in malignant lymphoma. In the first trial patients with NHL, Hodgkin's disease and CLL refractory to standard treatment were included. They received six courses with mitoxantrone 5 mg/m^2 weekly, with 9% response. In the second trial high-dose mitoxantrone was given three weekly only to patients with NHL. In this small group the response rate was 63%. Twenty-one previously untreated patients with low-grade NHL received single-agent therapy with mitoxantrone, 5 mg/m^2 daily for 3 days.[154] A high remission rate of 95% was obtained with a relapse-free survival of 68% at 2 years and all patients still alive. In a phase II study mitoxantrone was administered to 31 patients with refractory non-Hodgkin's lymphoma in a dose of 14 mg/m^2 every three weeks. The overall response rate was 47%, whereas in the doxorubicin pretreated part of the group it was 35%.[155]

In elderly people with unfavorable NHL, the feasibility of full-dose chemotherapy with mitoxantrone, cyclophosphamide, vincristine and prednisolone at four-week intervals was evaluated.[156] Thirty patients, with a mean age of 70.4 years, with untreated intermediate or high-grade malignant NHL or with refractory low-grade malignant NHL with bulky disease, were included. The overall response rate was 90% with a disease-free survival of 50% at one year. Toxicity apart from transient granulocytopenia was minor; even cardiac toxicity, evaluated with left ventricular ejection measurement in six patients with a history of cardiac illness, was not noted. The combination of mitoxantrone and Ara-C in 31 patients with refractory advanced NHL was studied by Ho *et al.*[157] An overall response of 45% was observed. Ho *et al.* performed a pilot non-randomized study with the same drug combination but a higher Ara-C dose in refractory

NHL.[57] One group of 23 patients treated in five centers received after chemotherapy recombinant human granulocyte–macrophage colony-stimulating factor (rh GM-CSF); the other group of 14 patients treated in four centers did not receive rh GM-CSF. The overall response in the group with rh GM-CSF was 65%, and in the group without rh GM-CSF was 43%. A reduced period of neutropenia and less stomatitis was observed in the group treated with rh GM-CSF vs the group without rh GM-CSF. A number of side-effects were probably related to rh GM-CSF. The combination of mitoxantrone, cisplatin and methylglyoxal bis-guanyl hydrazone was used as salvage therapy in a phase II trial in patients with malignant lymphoma.[158] The overall response rate was 34%, but severe granulocytopenia was common and fatal in 1/32 patients.

Reports about treatment of mitoxantrone in Hodgkin's disease are rather scarce with response rates of monotherapy mitoxantrone varying between 10% and 20%, generally concerning partial responses and small groups of patients.[159,160]

It can be concluded that mitoxantrone is an interesting drug in first-line and relapse NHL. There is no complete cross-resistance with the anthracyclines for this drug. Higher doses seem to be more effective than lower doses.

Other hematologic malignancies

Patients with multiple myeloma, refractory to standard chemotherapy, were treated with weekly mitoxantrone as single agent. The response rate of 5% was disappointing and hematologic toxicity was severe.[161] Preliminary results with the combination mitoxantrone, vincristine and dexamethasone in advanced refractory myeloma showed effectiveness of this regimen, but no definite conclusions could be drawn.[162]

Toxicity

Hematologic toxicity

Myelosuppression, predominantly granulocytopenia, is the major dose-limiting side-effect of mitoxantrone. Myelosuppression is dose dependent and is related to the amount of prior chemotherapy and/or radiotherapy and to the performance status of the patient. Probably the degree of bone marrow involvement of the tumor is also of influence.[163] Nadirs for white blood cells and platelets occur between eight and 15 days after therapy when mitoxantrone is given as single dose. WHO grade 4 leukocytopenia[164] was present in 2% of the patients[109] or 5–12% of the cycles,[116,165] whereas grade 4 thrombocytopenia occurred in less than 1%.[163,166] Myelosuppression was reversible, but dose reductions may be needed.[163,166] White blood cells measured before each new cycle of treatment and the corresponding white blood cells' nadirs fell until the fifth or sixth course and stabilized thereafter.[166] The mean platelet count decreased slightly up to the fifth or sixth successive course of therapy. The effect of mitoxantrone on red blood cells is limited; acute toxic effects are rare. Most patients developed a mild anemia with successive courses.[163,166]

Comparison of mitoxantrone with doxorubicin in breast cancer studies showed that the median leukocyte nadir was similar for mitoxantrone and doxorubicin during each course, but a dose reduction of doxorubicin was necessary with successive courses.[163] By the sixth course only 77% of the initial doxorubicin course could be prescribed vs 96% of the initial mitoxantrone dose. These results show that cumulative myelosuppression of mitoxantrone was in the same range as doxorubicin.

In a report of three patients who erroneously received large overdoses of a single bolus of mitoxantrone, two of them receiving 100 mg/m^2 and the third patient 183 mg/m^2, severe leukopenia was observed and platelet counts dropped in parallel with the white blood cells to levels $< 25 \times 10^9/1$, which urged the need for prophylactic platelet transfusions in two of them.[167] The hematologic toxicity, however, was reversible.

In vitro even low concentrations of mitoxantrone were toxic for hematopoietic precursor cells, which may explain the myelotoxicity of this drug.[168]

Cardiotoxicity

Mitoxantrone was brought to clinical trial in the expectation that it might be an effective substitute for doxorubicin without cardiac toxicity. However, cardiotoxicity was observed ranging from minor electrocardiographic changes to severe congestive heart failure.

Posner *et al.*[163] reported an overview of 4450 patients, in which the results of the 4000 patients of a previous study of Crossley[166] had been incorporated, treated with mitoxantrone from 1978 until 1985. Most of the 235 cardiac events reported occurred in patients with pre-existing risk factors, such as underlying heart disease, prior anthracycline

exposure and mediastinal radiation. In total 60 cases of congestive heart failure occurred. Most of them responded to diuretics and cardiac glycosides. Compared with doxorubicin mitoxantrone appeared to be less cardiotoxic.

Cardiac function tests, especially measurements of the left ventricular ejection fraction, were assessed by several investigators.[169–174] In many patients a decline in ejection fraction of less than 10–15% was observed, which was subclinical in the majority. Significant fall in ejection fraction, in general >15%, with clinical signs of congestive heart failure was rare and occurred after a cumulative mitoxantrone dose of about 160 mg/m^2 (range 82–243 mg/m^2). Other risk factors for congestive heart failure in these patients were not mentioned.

Endomyocardial biopsies were also performed in a number of studies[169,170,172] and showed changes similar to those after doxorubicin treatment including chromatin clumping, nucleolar contraction and swelling and degeneration of mitochondria and tubular structures. In one patient who received >200 mg/m^2, myofibrillar lysis was also demonstrated. Benjamin *et al.*[172] compared endomyocardial biopsies of patients treated with mitoxantrone who received prior doxorubicin or who did not receive this drug before. In the 37 patients without prior doxorubicin, electron microscopic findings in the endomyocardial biopsies were typical of those of early anthracycline cardiomyopathy. No dose-response correlation was seen within the cumulative dose range of mitoxantrone tested (40–206 mg/m^2). In the biopsies of the 29 patients with prior doxorubicin, who had received a median of 430 mg/m^2 of doxorubicin, the mean baseline biopsy grade was higher than that of the patients without prior doxorubicin after 80–100 mg/m^2 mitoxantrone. In this group there was some evidence of correlation between morphologic changes with increasing mitoxantrone dose, which strengthens the idea that mitoxantrone may potentiate pre-existing doxorubicin cardiomyopathy. In three patients with accidental overdose,[167] acute cardiac toxicity was not observed. One patient, who had prior daunorubicin at a cumulative dose of 760 mg/m^2, developed congestive heart failure after 4 months with satisfactory response to digitoxin and furosemide. The 2 other patients were not available for late cardiac complication because of early death due to tumor progression.

Recently, Ewer *et al.*[175] detected electrocardiographic changes in patients receiving mitoxantrone, pretreated with doxorubicin. A prolongation in QT interval was observed in patients who received a cumulative dosage of ≥400 mg/m^2 of doxorubicin and 60 mg/m^2 of mitoxantrone. QT interval prolongation may therefore be a helpful parameter in detecting cardiotoxicity, although further investigation of its usefulness seems necessary.

It can be concluded that cardiotoxicity after mitoxantrone can occur, but is less severe than after anthracycline therapy. For mitoxantrone a higher risk of fall in ejection fraction and of congestive heart failure is supposed after prior anthracyclines, mediastinal irradiation and cardiovascular disease. Endomyocardial changes are similar to those found after anthracycline therapy. There is no consensus on after which dose of mitoxantrone alone or after which dose of mitoxantrone in combination with prior anthracyclines is special caution for cardiotoxicity needed.[163,166,174,176] In the case of single-agent treatment with mitoxantrone after a cumulative dose of 160 mg/m^2, cardiac monitoring is indicated. In patients previously treated with anthracyclines, a cumulative dose level of >100 mg/m^2 of mitoxantrone requires cardiac function control.

Gastrointestinal

Nausea, vomiting and stomatitis are the most frequent non-hematologic toxicities. In general, these symptoms are mild to moderate.[162,166] and, compared with doxorubicin, mitoxantrone causes less frequent and less severe symptoms of nausea and vomiting. Nausea and vomiting do not occur in approximately 40% of patients. Diarrhea was in general tolerable and of short duration. Stomatitis and mucositis appeared to be dose dependent. In patients treated once weekly with mitoxantrone as single agent, the overall incidence was 10% (range 0.7–23%) and symptoms were mostly mild (soreness or erythema) or moderate (erythema and ulcers). When mitoxantrone is administered more frequently or at a higher dose level, as in hematologic malignancies and in bone marrow transplantation setting, stomatitis can become the dose-limiting side-effect.[57,58,166] More stomatitis and mucositis was observed of doxorubicin, in studies with single agent chemotherapy, as compared with mitoxantrone. In combination chemotherapy this difference was only small.[166]

Hepatic and pancreatic toxicity

Transient elevations of aminotransferases, bilirubins and alkaline phosphatase were reported after

single-agent or combination therapy with mitoxantrone.[142,152,177] This is an observation of special interest because mitoxantrone is metabolized by the liver and hepatic dysfunction may prolong serum half-life of the drug.

Finally, elevation of serum amylase and low back pain were noted in one patient after 100 mg/m^2 mitoxantrone, suggesting a reversible pancreatitis.[167]

Allergic reaction

Taylor *et al.*[178] reported three cases in which allergic-type reactions did occur. The first patient developed skin rash, with vasculitis in the skin biopsy respectively seven days and one day after her first and second mitoxantrone infusion. The second patient complained of breathlessness and feeling cold and was tachypnoeic and cyanotic and had unmeasurable pulse and blood pressure. She recovered after hydrocortisone and chlorpheniramine. Both had received no other medication and no history of allergy was present. A third patient had facial swelling and rash after the seventh and eighth course of mitoxantrone, which reoccurred later unrelated to any drug therapy. Siegert *et al.* observed shaking chills in two of the three patients with accidental overdose.[167]

Drug extravasation

During recent years some reports about extravasation of mitoxantrone have been published. Posner *et al.* reported only minimal irritation with erythema and mild swelling after accidental soft tissue infiltration.[163] Others noticed only transient blue staining of the skin. However, reactions can be more severe. Khoury described two patients of whom one patient developed an ulcer and the other developed severe induration and flexion deformity of the elbow. However, the patient with the ulcer also received mitomycin C which has vesicant properties and the contribution of mitoxantrone to this complication is therefore not very clear.[179,180] One patient with necrosis of the skin of the hand after extravasation of only mitoxantrone failed spontaneous healing, possibly as a result of continuation of chemotherapy.[181] Complete recovery occurred four months after cessation of chemotherapy and with local treatment. Extravasation along a catheter tract of a peritoneal Port-A-Cath resulted in a clinical picture very similar to Cullen's sign.[182]

Other toxicities

Alopecia is usually very mild; only very few patients experience moderate hair loss needing a wig. Even fewer patients reported complete loss of hair.[166] In two patients only loss of white hair was seen.[183] A slight dose–response correlation in the occurrence of alopecia seems present. Again, a considerable difference between mitoxantrone and doxorubicin is noted. Alopecia after mitoxantrone is reported in a range of 22–37% and after doxorubicin in a range of 68–80%.[116,165,166] After doxorubicin the alopecia is also more severe than after mitoxantrone. In combination chemotherapy regimens this difference was maintained.[166]

Ovarian dysfunction associated with mitoxantrone was reported by Schenkenberg and Von Hoff.[184] Direct toxic effects on the ovary were probably the explanation of this phenomenon; direct evidence (such as an ovarian biopsy) was not present.

Green or blue discoloration of urine has frequently been noted.[51,185] Also, discoloration of the nails has been reported.[186,187] Scheithauer *et al.*[186] reported two patients with transient mitoxantrone-related painless blue discoloration of fingernails and toenails. Onycholysis was not observed and nailbed hemorrhage due to mitoxantrone-induced thrombocytopenia could be excluded. In four patients, treated with alternating doxorubicin and mitoxantrone, first white painful nails were noted, followed by red–brown discoloration and onycholysis in three of them.[187] Transient painful onycholysis in two patients after single-agent therapy with mitoxantrone was also reported. The onycholysis in these patients necessitated discontinuation of the therapy.[188]

Conclusion

Mitoxantrone has especially antitumor activity in patients with breast cancer, leukemia and lymphoma. There is no complete cross-resistance in the clinic with the anthracyclines. It has an improved tolerability profile compared with doxorubicin. Dose-limiting toxicity is myelotoxicity and mucositis. Cardiotoxicity is less frequent than after doxorubicin and daunorubicin, but cardiotoxicity does occur. Indeed, mitoxantrone is like Bluebeard for some important malignancies.

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