The development of doxorubicin was an important advance in the treatment of patients with non-Hodgkin’s lymphoma (NHL). Alternatives to doxorubicin, such as mitoxantrone (Novantrone), have less nonhematologic toxicity and could offer a therapeutic advantage in some situations if similar antilymphoma activity exists. Several combination regimens that include mitoxantrone have been shown to be active.

The treatment of non-Hodgkin’s lymphoma (NHL) continues to be imperfect. With incidence increasing and the chance of cure at less than 50%, an improved understanding of NHL is needed, including which patients will benefit most from various treatments.[1] The American Cancer Society estimates that 53,900 new cases of NHL will be diagnosed in 2002, and 24,400 related deaths will occur. Both the incidence and mortality of NHL have been rising since the 1970s. Overall, survival rates are suboptimal, with 1-year survivals of 70% and 5-year survivals of only 51%.[2,3]

The ongoing effort to better understand NHL is reflected by the multiple modifications made to NHL classification systems over the past 2 decades. The World Health Organization (WHO) classification system is the most recently developed and is in line to replace the existing Working Formulation and Kiel classification systems.[4,5] The WHO classification reflects improvements in the understanding of the immune system, and is based on several factors, including histology, immune phenotype, genetic abnormalities, and clinical features.[6]

Mitoxantrone (Novantrone) is a cytotoxic anthracenedione, similar in structure to anthracyclines such as doxorubicin.[6] It inhibits topoisomerase II, interferes with RNA, and intercalates with DNA (resulting in strand breaks and cross-links) of which lead to cell death. Mitoxantrone is not cell-cycle specific.[6,7] It was developed in the 1970s as a more tolerable alternative to anthracyclines.[8] Early research established its activity alone and in combination with other chemotherapy agents against breast cancer, leukemia, and lymphoma. More recent studies have demonstrated its activity in the treatment of prostate cancer and in slowing the progression of multiple sclerosis.[7,8]

Specifically, the activity of mitoxantrone has been established against both follicular lymphomas and aggressive lymphomas, including diffuse large-cell lymphomas. In preliminary studies of follicular lymphoma, mitoxantrone at 14 to 18 mg/m² every 3 to 4 weeks yielded responses in previously treated patients (including those who had received doxorubicin), with complete response rates ranging from 6% to 16% and partial response rates from 38% to 56%.[9-11] Previously untreated patients with follicular lymphoma had slightly higher response rates, with a complete response rate of 29% and a partial response rate of 67%.[12]

Patients with relapsed or refractory aggressive lymphoma responded to lower doses of mitoxantrone (12 to 14 mg/m² every 3 to 4 weeks). The complete response rate ranged from 0% to 30% and the partial response rate, from 12% to 63%. Some of these patients had received previous treatment with doxorubicin.[9,10,13-16] This review will evaluate the current use of mitoxantrone in NHL, paying special attention to dose as it relates to outcome.

What Doses of Mitoxantrone and Anthracyclines Are Comparable?

Determining the optimal dose of mitoxantrone in NHL leads to a related question: What is the comparable dose of mitoxantrone and doxorubicin for use in NHL? The relevance of the question stems from the widespread use of doxorubicin in combination therapy for NHL, the high level of activity of both doxorubicin and mitoxantrone in NHL, and the fact that mitoxantrone is closely related to the anthracyclines pharmacologically.
Posner et al. reported that in early comparative trials of mitoxantrone and doxorubicin in breast cancer, a 5:1 ratio of doxorubicin to mitoxantrone was chosen based on data suggesting that this ratio would yield equally myelosuppressive doses of the drugs. Thus, when comparing CNF (cyclophosphamide [Cytoxan, Neosar], mitoxantrone [Novantrone], fluorouracil [5-FU]) to CAF (cyclophosphamide, doxorubicin [Adriamycin], 5-FU) in breast cancer, 10 mg/m² of mitoxantrone was compared to 50 mg/m² of doxorubicin. Single-agent comparisons used 12 to 14 mg/m² of mitoxantrone and 60 to 75 mg/m² of doxorubicin administered every 3 to 4 weeks.[17]

As described later in this review, the doses of mitoxantrone in combination therapy for NHL have ranged from 10 to 12 mg/m². Given that 12 mg/m² represents a 20% increase in dose intensity over the lower dose, an increase of 2 mg/m² could be an extremely important difference if there is a significant dose-response curve at this dose range.

Moderate reductions in the dose intensity of doxorubicin have produced a striking decrease in treatment outcome for breast cancer patients.[18] In the treatment of aggressive NHL, two studies found that 50 mg/m² of doxorubicin in the CHOP regimen (cyclophosphamide, doxorubicin HCl, vincristine, prednisone) was superior to 10 mg/m² of mitoxantrone in CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone),[19,20] and one study found the two regimens to be comparable.[21]

In a fourth trial, CNOP was found to be comparable to CHOP when the dose of mitoxantrone was increased to 12 mg/m² and compared to 50 mg/m² doxorubicin.[22] Similar results were observed in other regimens that substituted mitoxantrone, 12 mg/m², for doxorubicin, 50 mg/m²,[23] or mitoxantrone, 10 mg/m², for doxorubicin, 45 mg/m².[24,25] Therefore, the CNOP regimen should include mitoxantrone at 12 mg/m² if the goal is to achieve a therapeutic outcome comparable to that of CHOP with doxorubicin at 50 mg/m².

Are There Differences in Toxicity Between Mitoxantrone and Anthracyclines?

Patients receiving mitoxantrone experience less nonhematologic toxicity (alopecia, nausea, vomiting) than those receiving doxorubicin. This advantage may be particularly beneficial to patients such as the elderly, who may not tolerate full-dose doxorubicin therapy.

In early trials comparing mitoxantrone to doxorubicin (or CAF to CNF) in breast cancer, significantly lower rates of alopecia, nausea, vomiting, and stomatitis were reported in the mitoxantrone arm.[17] In later trials in lymphoma patients, in which a mitoxantrone-containing regimen was compared to a doxorubicin-containing regimen, the severity of alopecia was significantly reduced in many studies[19,20,22-26] or reported to occur less frequently.[21,27] Similarly, nausea and vomiting were significantly reduced in trials comparing a mitoxantrone regimen to a doxorubicin regimen,[19,20] with one trial reporting significantly less mucositis in the mitoxantrone arm.[19]

Studies have shown that the cardiotoxicity associated with mitoxantrone is qualitatively similar to that associated with the anthracyclines, and is more likely to appear after cumulative mitoxantrone doses of 160 mg/m², or 100 mg/m² if the patient has received previous anthracycline therapy.[28] Although mitoxantrone may be less cardiotoxic than doxorubicin at comparable cumulative doses, caution is necessary because cardiotoxicity can also occur at low doses of mitoxantrone. Patients who have previously received doxorubicin or mediastinal irradiation, or who have underlying cardiac disease, will be at greater risk for mitoxantrone-associated cardiotoxicity.[6,7]

Mitoxantrone in Diffuse Large-Cell NHL

Primary Therapy

Table 1 illustrates data from first-line regimens using mitoxantrone in patients with diffuse large-cell lymphomas.[19-25,29-36] An early trial established the activity of CNOP administered every 3 weeks to 13 patients, with an overall response of 85%.[29] More recently, CNOP administered to 373 patients through a community-based oncology network resulted in a complete response rate of 60%.
and an overall response rate of 73%.[30] Comparative trials of mitoxantrone-based vs doxorubicin-based regimens as primary therapy are also listed in Table 1.

Varying results have been reported after mitoxantrone, 10 mg/m², was substituted for doxorubicin, 50 mg/m², in the CHOP regimen. Pavlovsky et al reported no difference in complete, overall, or event-free survival when CNOP or CHOP was given every 3 to 4 weeks.[21] This finding contrasts with the results of a later trial in which patients receiving CHOP had a significantly better complete response rate. However, there was no advantage in the latter trial in terms of survival or relapse, when CHOP or CNOP cycles were administered every 3 weeks.[19]

When the regimens were administered every 4 weeks, CHOP resulted in significantly better complete response and survival rates, including lymphoma-specific survival at 3 years. Among patients entering a complete response, there was no significant difference between the CHOP and CNOP arms in the median disease-free interval.[20] A fourth CNOP/CHOP comparative trial used mitoxantrone at 12 mg/m² vs doxorubicin at 50 mg/m²; the regimens were administered every 3 to 4 weeks. Results between arms were comparable, and there were no significant differences in complete response rate, 2-year overall survival, or relapse-free survival.[22]

Three trials reported significantly less alopecia associated with CNOP, regardless of the mitoxantrone dose.[19,20,22] Pavlovsky et al also reported less severe alopecia in the CNOP arm, but the difference was not statistically significant.[21] However, other nonhematologic toxicities were significantly lower in patients receiving CNOP. These included less severe nausea, vomiting,[19,20] and mucositis,[19] and fewer patients with a greater than 10% decrease in the left-ventricular ejection fraction (40% with CHOP vs 7% with CNOP, P < .039).[22] Cardiomyopathy risk factors did not appear to differ between the CNOP and CHOP groups.

Mitoxantrone substituted for doxorubicin in other regimens has yielded comparable response and survival rates. Vose et al included 12 mg/m² of mitoxantrone in the CMP-BOP regimen (cyclophosphamide, mitoxantrone, procarbazine [Matulane], oral bleomycin [Blenoxane], vincristine, prednisone), comparing it to two variants of CAP-BOP (cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine, prednisone) using 50 mg/m² doxorubicin.[23] Complete response, overall response, 3-year overall survival, and failure-free survival rates were not significantly different between groups. However, patients older than 70 who received a one-third dose reduction had a significantly worse failure-free survival compared to younger patients (age 60 to 70) receiving full-dose therapy. Patients in the CMP-BOP arm experienced significantly less alopecia than did patients in either CAP-BOP arm (38% vs 100%, P < .01).

Two earlier trials compared m-BNCOD (methotrexate, bleomycin, mitoxantrone, cyclophosphamide, vincristine, dexamethasone) to m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) administered every 21 days.[24,25] In these studies, the doses of mitoxantrone and doxorubicin were 10 mg/m² and 45 mg/m², respectively. There were no significant differences in response or survival rates between groups. Nonhematologic toxicity was similar, with the exception of alopecia, which occurred significantly less often in both studies in patients receiving the mitoxantrone regimen. In addition, after 10 cycles of treatment, Guglielmi et al reported that six cardiac events worse than WHO grade 1 were reported in the m-BNCOD arm, whereas no episodes of the same grade occurred in the m-BACOD arm.[25]

Salvage Therapy

Early trials demonstrating the activity of mitoxantrone combined with ifosfamide (Ifex)[37,38] led to variations of the MINE regimen (mesna [Mesnex], ifosfamide, mitoxantrone, etoposide) including MINT, in which paclitaxel (Taxol) is substituted for etoposide. MINE has also been followed by various consolidation regimens to improve response (see Table 2).[37-46] Doses of mitoxantrone in these studies have ranged from 8 to 12 mg/m². Mitoxantrone at 12 mg/m² with ifosfamide every 3 to 4 weeks yielded a complete response rate of 30% to 38% in patients refractory to or relapsing after doxorubicin or epirubicin (Ellence)-based regimens, many of whom received mitoxantrone/ifosfamide as third- or fourth-line therapy. As expected, few primarily refractory patients achieved a complete response; most responders were in relapse after previous therapy.[37,38]
Other regimens utilizing a mitoxantrone dose of 12 mg/m² include MINE as first-line therapy[39] and MINE given sequentially with CANP (cyclophosphamide, doxorubicin, vinorelbine [Navelbine], prednisone).[40] In previously untreated patients, mitoxantrone at 12 mg/m² as part of the MINE[39] or MINE-CANP regimen[40] resulted in complete response rates of 56% and 72%, respectively. MINE as first-line therapy was well tolerated with mild myelosuppression, nausea, vomiting, and alopecia, and a promising overall survival in responding patients of 80% at 4 years.[39] After six cycles of MINE-CANP, 72% of patients achieved a complete response.[40]

Dincol et al administered mitoxantrone as a flat dose of 20 mg per cycle as part of the MINE-BOP regimen. The addition of nonmyelosuppressive drugs (bleomycin, vincristine, prednisone) to MINE did not improve response or survival compared to MINE alone.[41]

A lower dose of mitoxantrone (8 mg/m²) was used as part of MINE consolidated with ESHAP (etoposide, methylprednisolone [SoluMedrol], high-dose cytarabine, cisplatin)[42,43] MINT,[44] or MINT-ESHAP.[45] The dose of mitoxantrone was reduced to decrease the likelihood of severe myelosuppression from the addition of ESHAP or paclitaxel. Nevertheless, the most common toxicity was myelosuppression, leading infrequently to severe infection. MINE-ESHAP appears to be active across histologic subtypes and results in a durable complete response.[42] MINT-ESHAP appeared comparable to MINE-ESHAP after differences in prognostic factors were taken into account.[45]

The response and survival data for mitoxantrone, etoposide, and various corticosteroid combinations are highlighted in Table 3.[27,47-54] Most studies included previously treated patients and found a wide range of complete (9% to 50%) and overall responses (38% to 67%). As expected, complete response rates were better in two first-line trials (63% and 69%),[27,47] with a high overall response of 91% in patients receiving ENAP (etoposide, mitoxantrone, cytarabine [Ara-C], prednisone) followed by CHOP.[47] Two trials of mitoxantrone, etoposide, and prednisone or prednisolone used higher mitoxantrone doses (14 mg/m² every 3 weeks[48] or 18 mg/m² administered in divided doses over 3 days).[49]

In the first trial, 61 of 79 patients had received previous CHOP therapy and were considered ineligible for high-dose chemotherapy; mitoxantrone and etoposide were chosen due to an apparent lack of cross-resistance to anthracycline-containing regimens. This outpatient regimen resulted in an overall response of 38% and was considered comparable to other salvage regimens. It was well tolerated, with moderate hematologic toxicity. Notably, in the subset of patients more than 60 years old, the complete and overall response rates were superior to those in younger patients: 19% vs 9% and 67% vs 38%, respectively. Overall survival at 2 years was also better in the elderly group (49% vs 31%). These differences may have been the result of the younger patients having received more extensive previous treatment.[48]

In the second study in younger patients (median age: 54 years) in whom first-line anthracycline-based regimens failed, 10 of 20 patients achieved a complete response in the third treatment cycle, with 5 patients remaining in complete response at 23 to more than 35 months. Acute toxicity was mild, with myelosuppression as the primary toxicity.[49] Thus, mitoxantrone is effective as salvage therapy, even in patients refractory to or relapsing following anthracycline front-line therapy.

Use in the Elderly

Mitoxantrone regimens that have been specifically developed for use in the elderly, designed to maintain efficacy while concomitantly reducing toxicity, are described in Table 4a and Table 4b.[20,31,55-69] Age is an important prognostic factor in NHL. This may be partly due to the fact that elderly patients are not often able to tolerate full-dose anthracycline-based regimens.[55,56] Mitoxantrone was substituted for doxorubicin because of its high level of activity in NHL and the potential for reduced nonhematologic toxicity.

Single-arm trials of CNOP in the elderly have produced high complete response rates, ranging from 60% to 75%.[57-59] Two trials studied mitoxantrone at 10 mg/m²,[57,58] while a third trial used a mitoxantrone dose of 12 mg/m² every 3 weeks[59]; all three trials reported acceptable toxicity.
Experience at the Nebraska Lymphoma Study Group supports the use of mitoxantrone at 12 mg/m² in the CNOP regimen. More than 370 previously untreated patients have received CNOP every 3 weeks in an outpatient program. Response rates have been comparable to those achieved with doxorubicin-based regimens (complete response: 60%, overall response: 73%) with less nonhematologic toxicity. The 5-year estimated overall survival was 44% for patients older than 60, compared to 62% for patients younger than 60 \( (P < .001) \).[30]

In two trials in previously untreated elderly patients, CHOP resulted in a significantly better response than CNOP. A mitoxantrone dose of 10 mg/m² was used in both trials.[20,31] Sonneveld et al reported a significantly better complete response rate (49% vs 31%, \( P = .03 \)) and overall survival (26 vs 12 months, \( P = .03 \)) for patients in the CHOP arm. The disease-free interval and survival were similar for patients who achieved a complete response on either CHOP or CNOP. The regimens in this study were equitoxic; however, it was suggested that the dose of mitoxantrone may have been too low, with the author citing single-arm studies that had used a dose of 12 to 14 mg/m².[20] In the second trial, CHOP, with or without granulocyte colony-stimulating factor (G-CSF [Neupogen]) support, produced a significantly better complete response rate (60% vs 43%, \( P < .001 \)) and survival than CNOP.[31]

### Mitoxantrone in Follicular NHL

Follicular lymphoma usually responds well initially to chemotherapy; however, these responses are typically not durable, as evidenced by the incidence of relapse and the need for further treatment. Mitoxantrone, in combination with fludarabine (Fludara) and with or without dexamethasone, has demonstrated activity in previously untreated patients and those with recurrent or refractory disease.

### Primary Therapy

The first studies to combine mitoxantrone and fludarabine in follicular lymphoma also included dexamethasone, forming the FND regimen. Recently, investigators have omitted dexamethasone when mitoxantrone and fludarabine are combined for primary treatment, thus reducing the occurrence of infection and associated morbidity. In two studies of fludarabine at 25 mg/m² on days 1 to 3 and mitoxantrone at 10 mg/m² on day 1 in advanced follicular lymphoma and small lymphocytic lymphoma, the overall response rate ranged from 89% to 91%, with a high proportion of patients entering complete response (67% and 43%).[70,71] Velasquez et al reported a progression-free survival at 2 years of 63% with an overall survival of 93%. Patients with a serum beta-2-microglobulin greater than 2.5 mg had a lower complete response rate (21%) and lower 2-year progression-free survival (47%).[49] Specifically, in the subset of follicular lymphoma patients, the overall response was 94%, complete response, 76.5%, estimated 2-year relapse-free survival, 83%, and overall survival, 92%. An additional trial comparing FN (fludarabine, mitoxantrone) to CHEP (cyclophosphamide, doxorubicin HCl, vindesine [Eldisine], prednisone) in advanced follicular lymphoma patients (stage II bulky, III, or IV low-grade lymphoma) found that FN produced a significantly better complete response rate than CHEP at both 6 months (32% vs 3%, \( P = .0035 \)) and 12 months (44% vs 22%, \( P = .023 \)).[72]

Another primary treatment approach compared PmM (prednimustine, mitoxantrone) to COP (cyclophosphamide, vincristine, prednisone). The overall response was similar between groups; however, the complete response rate was significantly better in patients receiving PmM (36% vs 18%, \( P < .006 \)). This study enrolled patients with both follicular lymphoma and mantle cell lymphoma and resulted in a trend toward a higher complete response rate in the follicular lymphoma patients (30% vs 16%). PmM also resulted in a longer event-free interval than COP (31 vs 14 months, \( P = .04 \)). PmM was more myelotoxic, but COP resulted in more alopecia and peripheral neurotoxicity.[26]

In another trial, patients with stage IV indolent lymphoma were randomized to receive an intensive, alternating triple therapy (ATT) regimen—CHOD-Bleo/ESHAP/NOPP (cyclophosphamide, doxorubicin, vincristine, dexamethasone, bleomycin/etoposide, methylprednisolone, cytarabine,
cisplatin/mitoxantrone, vincristine, procarbazine, prednisone) or FND. All patients then received 1 year of maintenance therapy with interferon and dexamethasone. Responses were comparable between arms (overall response with ATT: 97%, with FND: 99%; complete response with ATT: 85%, with FND: 81%). Failure-free survival was significantly longer in the ATT arm compared to the FND arm (56 vs 45 months, \( P = .01 \)) but there was more grade 3/4 hematologic toxicity in patients receiving ATT.[73]

Salvage Therapy

Several studies have demonstrated the activity of the mitoxantrone regimens in relapsed and refractory follicular lymphoma (Table 5).[47,60,74-87] In a phase I study, McLaughlin et al found that FND produced a response at all dose levels, with a complete response rate of 43% and an overall response rate of 74%.[74] A subsequent phase II trial evaluated FND administered every 4 weeks (fludarabine, 25 mg/m² on days 1 to 3; mitoxantrone, 10 mg/m² on day 1; dexamethasone, 20 mg/d on days 1 to 5). Patients had received one to more than four previous regimens, and most had received prior doxorubicin. Of 51 patients, 14 had also received mitoxantrone more than 12 months prior to enrollment.

FND was highly active, producing an overall response rate of 94%; the median failure-free survival was 21 months. Primary toxicities included myelosuppression and infection. Infection occurred in 12% of courses, or 30 episodes, 13 of which were opportunistic infections prompting the use of prophylactic trimethoprim/sulfamethoxazole to prevent pneumocystis pneumonia.[75]

In two studies in which prednisone was substituted for dexamethasone,[76,60] responses were similar to those reported by McLaughlin et al, with rapid response noted after two to three courses. Myelosuppression and infection were also a problem, with all major infections occurring in the respiratory tract or sinuses.[60] A poorer response (complete response: 20%, overall response: 69%) was reported by Crawley et al, most likely due to the inclusion of more primarily resistant patients.[77] FN every 4 weeks as salvage therapy resulted in fewer infections; however, neutropenia was still the primary toxicity.[78]

The combination of mitoxantrone or doxorubicin with cladribine (Leustatin) synergistically induces apoptosis in both normal and neoplastic lymphocytes.[88] An earlier phase I trial using a low dose of mitoxantrone (5 mg/m²) also confirmed the activity of mitoxantrone in combination with cladribine.[79] A combination of dexamethasone, mitoxantrone, 10 mg/m², and cladribine every 4 weeks resulted in myelosuppression, infection, and a poor response (complete response: 7%, overall response: 29%).[80] The addition of G-CSF and a longer dosing interval of 4 to 6 weeks ameliorated the hematologic toxicity somewhat and decreased the occurrence of infection. The response rate also improved, with a complete response of 33% and an overall response of 80%.[81]

Rummel et al administered cladribine and mitoxantrone at 16 mg/m² over 2 days to untreated patients or mitoxantrone at 12 mg/m² to patients in relapse. An overall response of 88% and a complete response of 38% prompted investigators to begin a randomized trial comparing mitoxantrone and cladribine to chlorambucil (Leukeran), mitoxantrone, and prednisone.[82]

Mitoxantrone Plus Antibodies

The benefits of combining mitoxantrone and rituximab (Rituxan) have been explored in several recent preliminary studies. Rituximab is a monoclonal anti-CD20 antibody that has single-agent activity against B-cell lymphomas. Rituximab lacks myelosuppressive effects, and thus, is a good choice for combination therapy with an agent such as mitoxantrone.

As primary therapy for low-grade lymphoma, six cycles of FN (mitoxantrone, 12 mg/m²) followed by 4 weeks of rituximab resulted in an overall response of 86% (12/14). Of six patients with follicular lymphoma, three achieved a partial response and three entered complete response.[89] In another trial, two cycles of mitoxantrone and cyclophosphamide were followed by four cycles of rituximab and mitoxantrone. Of 13 patients with follicular lymphoma, 11 entered complete response, and one had a partial response. The overall response in other indolent subtypes was similarly promising: Four of five patients with small lymphocytic lymphoma, all four with lymphoplasmacytic lymphoma, and
all five with marginal cell lymphoma responded. This good response was not totally unexpected, however, as a majority of patients were previously untreated.[90]

In relapsed follicular lymphoma, four monthly cycles of FN followed by four weekly doses of rituximab yielded a complete response rate of 60% (9/16) and partial response rate of 33% (5/16). Although there was no effect on overall response, the addition of rituximab increased the complete response rate from 31% following FN to 60% following rituximab. Of 10 patients with a positive polymerase chain reaction (PCR) t(14;18) translocation, 8 achieved a molecular remission.[91] A high overall response rate of 90% was again observed when rituximab was combined with ifosfamide, mitoxantrone, and etoposide (RIME) plus G-CSF support as an induction and mobilization regimen. An added benefit of rituximab was the observed reduction of tumor cell contamination in the stem cell product harvested for possible autotransplant.[92]

**Mitoxantrone in AIDS-Related NHL**

The optimal treatment of acquired immunodeficiency syndrome (AIDS)-related NHL is not yet defined; combination chemotherapy with mitoxantrone has been used with varying results. In one study, 21 previously untreated patients received a regimen of CNOP plus G-CSF. Mitoxantrone was substituted for doxorubicin to reduce the likelihood of nausea, cardiotoxicity, and alopecia. The response was disappointing, with an overall response of 43% (complete response: 19%, partial response: 24%) and a median survival of only 5 months.[93]

The lack of studies of second-line treatment in AIDS-related NHL patients prompted the prospective study of VMP (etoposide [VePesid], mitoxantrone, and prednimustine every 3 weeks) in 21 consecutively enrolled patients; 13 patients were resistant and 8 had relapsed after receiving anthracycline-containing regimens. The overall response was 37% (7/19), with five evaluable patients (26%) entering complete response and four of the complete responses occurring in relapsed patients. The overall median survival was disappointing (2 months); however, patients in complete response had a significantly longer median survival of 13 months.[94]

An important question concerns the effect of concomitant use of antiretroviral therapy with chemotherapy on the response to chemotherapy. In one study comparing didanosine (ddl, Videx) and chemotherapy to chemotherapy alone, didanosine did not improve response or survival when added to a regimen of cyclophosphamide, mitoxantrone, etoposide, bleomycin, and vincristine. The complete response and survival rates were almost identical between groups.[95] However, in a later trial in 29 patients in which triple antiretroviral therapy was added to a regimen of cyclophosphamide, vincristine, mitoxantrone, bleomycin, and G-CSF, the triple antiretroviral therapy appeared to allow adequate doses of chemotherapy to be administered with fewer opportunistic infections. This resulted in a complete response rate of 72%, 3-year time to treatment failure of 85%, disease-free survival of 62%, and overall survival of 55%. [96]

**Mitoxantrone Plus Stem Cell Transplant**

High doses of mitoxantrone (60 to 90 mg/m²) in combination with other chemotherapy agents have been successfully administered to lymphoma patients as preparative regimens for hematopoietic stem cell transplantation. In patients with refractory lymphoma, Attal et al administered a conditioning regimen of mitoxantrone, in escalating doses of up to 75 mg/m², in combination with CBV (cyclophosphamide, carmustine [BiCNU], etoposide).[97] Of 11 patients with NHL and Hodgkin’s disease, 8 who received at least 60 mg/m² of mitoxantrone achieved a complete response, with none of these patients relapsing at 16 months. The toxicity of mitoxantrone in combination with CBV was acceptable, primarily including neutropenia, thrombocytopenia, and mucositis.

In previously treated follicular lymphoma patients, HAM (high-dose cytarabine, 4 g/m²/d on days 1 and 2, and mitoxantrone, 10 mg/m²/d on days 2 and 3) followed by peripheral blood stem cell transplant induced a response in 39 of 48 patients, all of whom remained in remission at 15 months. Of the remaining nine patients, seven relapsed at 5 to 29 months and two died of transplant-related complications.[98]
In another trial, 14 of 15 relapsed follicular lymphoma patients receiving mitoxantrone at 60 mg/m² plus melphalan (Alkeran) at 180 mg/m² achieved a clinical complete response, and 11 remained in complete clinical and molecular remission at a median follow-up of 3 years.[99] The same doses of mitoxantrone and melphalan followed by peripheral blood stem cell transplant resulted in a 2-year progression-free survival of 44% in patients with aggressive NHL. This regimen was also well tolerated; nausea and mucositis were the most frequently reported nonhematologic toxicities.[100]

As a means of increasing dose intensity and improving response, tandem regimens of sequential high-dose chemotherapy including mitoxantrone and melphalan[101-104] or mitoxantrone, carmustine, cyclophosphamide, and etoposide[104] have resulted in complete response rates ranging from 58% to 90%. In one of these studies in follicular lymphoma patients receiving sequential high-dose mitoxantrone and melphalan, long-term follow-up at a median of 4.3 years showed the estimated 9-year overall and event-free survival rates to be 84% and 45%, respectively.[103]

As initial treatment for diffuse lymphoma, Schenkein et al reported a 78% overall and 67% relapse-free survival at 18 months.[101] Of nine patients with poor-prognosis NHL, six remained in complete response at 100 days following the second transplant,[104] while 90% of patients with aggressive NHL achieved a complete response following tandem regimens of mitoxantrone/melphalan and etoposide/carboplatin (Paraplatin).[102]

Conclusions

Trials have consistently demonstrated that mitoxantrone is effective and well tolerated in patients with both diffuse large-cell lymphoma and follicular lymphomas. Mitoxantrone- and ifosfamide-based regimens are effective as salvage therapy in diffuse large-cell lymphoma. Data from combinations of mitoxantrone and etoposide support the lack of complete cross-resistance between mitoxantrone and anthracycline-based regimens, suggesting a role for mitoxantrone as salvage therapy for patients refractory to or relapsing following anthracycline front-line therapy.

Mitoxantrone combinations also retain efficacy in the elderly and are usually well tolerated in terms of nonhematologic toxicity. When mitoxantrone, 12 mg/m², is substituted for doxorubicin, 50 mg/m², the results of primary therapy in patients with diffuse aggressive lymphoma appear comparable.

In follicular lymphoma, combinations of mitoxantrone, fludarabine, and a corticosteroid show activity as salvage therapy, as long as infectious complications are reduced either by administering prophylactic antibiotic therapy or eliminating the corticosteroid. Future studies will determine the value of mitoxantrone in combination with cladribine and rituximab. When antilymphoma activity is found to be comparable, the apparently lower nonmyeloid toxicity seen with mitoxantrone could provide a therapeutic advantage.

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