The Role of Mitoxantrone in the Treatment of Indolent Lymphomas

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ABSTRACT

With the introduction of newer therapeutic approaches, survival in indolent non-Hodgkin’s lymphoma (NHL) appears to be improving. Mitoxantrone (Novantrone®; Serono, Inc.; Rockland, MA, http://www.seronousa.com), an anthracenedione with low cardiotoxic potential, has demonstrated activity in indolent NHL in combination with fludarabine (Fludara®; Berlex Laboratories; Wayne, NJ, http://www.berlex.com) and other agents. In a Southwest Oncology Group trial (SWOG 9501), treatment with fludarabine and mitoxantrone (FM) induced a complete remission (CR) rate of 44% and a partial remission (PR) rate of 50% in untreated patients. The estimated 4-year progression-free survival (PFS) rate was 38%. In a multi-center Italian trial comparing the efficacy of FM with that of cyclophosphamide, doxorubicin (Adriamycin®; Bedford Laboratories; Bedford, OH, http://www.bedfordlabs.com), vincristine ( Oncovin®; Eli Lilly and Company; Indianapolis, IN, http://www.lilly.com), and prednisone (Deltasone®; Pfizer Pharmaceuticals; New York, NY, http://www.pfizer.com), CHOP, followed by rituximab (Rituxan®; Genentech, Inc.; South San Francisco, CA, http://www.gene.com) for patients with incomplete clinical or molecular responses, the CR and molecular response rates were significantly higher in the FM arm, but the PFS and overall survival (OS) rates did not differ between the two arms. However, FM was also significantly less toxic than CHOP. The administration of rituximab following chemotherapy resulted in higher clinical and molecular...
response rates in both arms. In a separate trial, FM plus dexamethasone (Decadron®; Merck and Co., Inc.; Whitehouse Station, NJ, http://www.merck.com), FND, plus concurrent rituximab produced a CR rate of 92%. In a randomized German study, patients with indolent lymphomas received FM plus cyclophosphamide (FCM) or FCM with rituximab. PFS and OS times were significantly better for patients who received combined chemoimmunotherapy. Mitoxantrone-based regimens are highly active and well tolerated in patients with both relapsed and previously untreated indolent lymphomas. The addition of rituximab appears to increase the activity of the FM, FND, and FCM regimens. Although the results of the Italian multicenter study support the superiority of FM over CHOP in terms of clinical and molecular responses and tolerability, additional studies using rituximab in combination with both of these regimens should be attempted to determine the possible further benefit of both in the management of indolent lymphoma. Because cure remains elusive in patients with indolent lymphoma, maximum prolongation of PFS with minimal toxicity and maximum preservation of quality of life should remain central goals of treatment.

**INTRODUCTION**

Indolent lymphomas constitute 30%–35% of all non-Hodgkin’s lymphoma (NHL) subtypes. Of these, follicular lymphoma is the most common form of indolent lymphoma, found in the vast majority of patients [1, 2]. Approximately 54,000 new cases of NHL are expected in the U.S. in 2004 [3]. For reasons that are incompletely understood, the incidence of NHL has been rising over the past 10 years, with the sharpest rate of increase in individuals aged 65 years and older [4]. As the population ages, the incidence of NHL is expected to further increase. For this reason, more patients with indolent NHL may be expected to have significant medical comorbidities in the future, creating new challenges to therapy of these diseases.

Historically, the course of indolent lymphoma is characterized by initial responsiveness to a variety of treatment approaches, with good response rates, but frequent relapses. Most patients with indolent lymphomas appear to have diseases that progress so slowly that delayed treatment is a management option, justifying a “watch and wait” approach to the initial treatment. However, over time, clinical progression occurs in almost all patients, and median survival rates with standard regimens such as cyclophosphamide, doxorubicin (Adriamycin®; Bedford Laboratories; Bedford, OH, http://www.bedfordlabs.com), vincristine (Oncovin®; Eli Lilly and Company; Indianapolis, IN, http://www.lilly.com), and prednisone (Deltasone®; Pfizer Pharmaceuticals; New York, http://www.pfizer.com), CHOP, range from 5–10 years in large series [1, 2, 5, 6]. More recently, with the introduction of newer therapeutic approaches, improved 10-year survival rates (37%–60%) have been reported in some studies [7]. A recent trial using combination therapy with fludarabine (Fludara®; Berlex Laboratories; Wayne, NJ, http://www.berlex.com), mitoxantrone (Novantrone®; Serono, Inc.; Rockland, MA, http://www.serounda.com), and dexamethasone (Decadron®; Merck and Co., Inc.; Whitehouse Station, NJ, http://www.merck.com), FND, plus rituximab (Rituxan®; Genentech, Inc.; South San Francisco, CA, http://www.gene.com) demonstrated a 3-year overall survival (OS) rate of 95% and a 5-year failure-free survival (FFS) rate of 70% [8, 9]. Additional studies are required to confirm these findings.

Current National Comprehensive Cancer Network (NCCN)-recommended regimens for the first-line treatment of follicular lymphoma include: single-agent therapy with rituximab, chlorambucil (Leukeran®; GlaxoSmithKline; Philadelphia, PA, http://www.gsk.com), or cyclophosphamide; single-agent fludarabine with or without rituximab; combination treatment with cyclophosphamide, vincristine (Oncovin®; Eli Lilly and Company), and prednisone (Deltasone®; Pfizer Pharmaceuticals), CVP, or CHOP with or without rituximab; and combination treatment with FND with or without rituximab. Because the choice of initial therapy is influenced by multiple factors, such as age, patient comorbidities, and future treatment possibilities (e.g., autologous stem cell transplant), treatment selection may be individualized. Recommendations for second-line treatment include: radioimmunotherapy, for patients who have had no prior stem cell transplant and have adequate bone marrow reserve; autologous or allogeneic stem cell transplant; and chemoimmunotherapy regimens, as described for initial therapy (Table 1) [10].

Recent studies suggest that molecular response may be an important correlate of ultimate outcome in patients with indolent lymphomas. The \( bcl-2 \) gene is rearranged in 80%–90% of patients with follicular lymphomas, leading to overexpression of the Bcl-2 protein. This overexpression of Bcl-2 is caused by the chromosomal translocation t(14;18), which results in juxtaposition of the \( bcl-2 \) gene with immunoglobulin heavy chain gene enhancer elements. Possible consequences of Bcl-2 overexpression include increased longevity of malignant cells and resistance to many chemotherapeutic agents. \( bcl-2 \) gene rearrangements can frequently be detected by the polymerase chain reaction (PCR). Using this technique, patients can be tested for evidence of minimal residual disease (MRD) following treatment. The PCR assay is capable of detecting one lymphoma cell bearing the \( bcl-2 \) rearrangement in as many as several hundred thousand normal cells [11]. The
achievement of molecular response, or remission, defined as the disappearance of bcl-2 amplicons in peripheral blood or marrow following initiation of therapy in a patient with known baseline bcl-2 rearrangements, has been associated with superior clinical outcome, and reversion to a negative bcl-2 status in blood or bone marrow (molecular remission) tends to correlate with longer clinical remission. Although nodal relapses can occur in patients who are bcl-2 negative as assessed by PCR assay, a significantly longer FFS has been reported for patients with follicular lymphomas who achieved molecular responses within their first year of treatment, compared with those who did not (4-year FFS rates: 76% and 38%, respectively; \(p < .001\)) [11].

In this report, we review recent data on the use of mitoxantrone-containing regimens in the treatment of indolent NHL.

### Indolent Lymphomas: Single-Agent Therapies

A variety of drugs are active in the treatment of indolent lymphomas both as single agents and in combination with other drugs. Single-agent therapy has been employed as a standard of treatment in indolent lymphoma for many years. The characteristics of mitoxantrone in combination with several agents suggest that this drug has significant activity in the treatment of indolent lymphomas.

#### Mitoxantrone

Mitoxantrone, an anthracyclene compound, has a spectrum of clinical activity similar to that of the anthracyclines. It lacks the amino sugar of doxorubicin and the characteristic ring structure of classical anthracyclines. On the basis of these modifications, it was predicted that mitoxantrone would retain the antineoplastic activity of the anthracycline class with less potential for cardiotoxicity [12, 13]. Preclinical studies demonstrated that mitoxantrone inhibits topoisomerase II, interferes with RNA synthesis, and intercalates with DNA, resulting in strand breaks and crosslinking [12, 14]. Mitoxantrone also has demonstrated potent activity in preclinical lymphoma models and appears clinically active against both aggressive and follicular lymphomas [15–17].

Mitoxantrone is clinically associated with a much lower cardiotoxic risk than is doxorubicin. Although the mechanism of mitoxantrone-induced cardiotoxicity is not certain, anthracycline-associated cardiotoxicity appears to be caused by activated oxygen-free radicals; in vitro, mitoxantrone has been shown to generate free radicals to a much lesser degree than doxorubicin [18]. In a comparative trial of patients with advanced breast cancer treated with either cyclophosphamide, doxorubicin, and fluorouracil (CAF) or cyclophosphamide, mitoxantrone, and fluorouracil (CNF), investigators observed significantly less cardiotoxicity in the group receiving CNF [13].

#### Fludarabine

Fludarabine, one of the purine analogues, is an antimetabolite with significant activity against chronic lymphocytic leukemia and indolent lymphomas. Phase I and phase II trials of fludarabine in patients with relapsed and refractory follicular lymphomas demonstrated response rates of 30%–60% [19–21]. When combined in vitro, fludarabine and mitoxantrone exert synergistic effects [22]. In a study of patients with relapsed or refractory indolent lymphomas...
who received fludarabine, mitoxantrone, and dexamethasone, complete response (CR) and partial response (PR) rates were 47% and 47%, respectively. Acute nonhematologic toxicities, such as nausea and vomiting, were modest. The major adverse effect was myelosuppression. Opportunistic infections with *Pneumocystis carinii* and Herpes zoster were seen. On the basis of these promising results, investigators began clinical trials of FND in previously untreated patients with indolent lymphomas [23].

**Rituximab**

Rituximab, a chimeric mouse/human antibody directed against CD20, is an important therapeutic option for patients with B-cell lymphomas. In preclinical studies, rituximab lysed CD20+ cells via human-complement or antibody-dependent cell-mediated cytotoxicity and induced apoptosis in the presence of either goat antimouse IgG or Fc receptor–expressing cells [24]. Many investigators have demonstrated that single-agent rituximab has significant clinical activity in pretreated patients with follicular lymphomas. In one study, patients with follicular lymphomas who received first-line single-agent rituximab had a clinical response rate of 73% and a molecular response rate of 62% at 1 year [24]. Rituximab has now been combined with many different chemotherapy regimens. When this antibody was combined with CHOP, CRs were seen in 50%–60% of patients and PRs were seen in 30%–40% [25–28]. Similar synergy was observed when rituximab was combined with fludarabine both in vitro and in vivo [27]. These regimens, and others, appear to result in longer disease-free survival times for patients with indolent lymphomas when compared with patients who receive chemotherapy alone. However, no study has unequivocally demonstrated superior survival rates using the combination of rituximab and chemotherapy. Toxicities following rituximab chemotherapy combinations were generally similar to those occurring with these regimens when administered without rituximab, indicating an absence of overlapping toxicities.

**Cyclophosphamide**

Cyclophosphamide, the most frequently used alkylating agent in the treatment of lymphomas, was first described as therapy for diffuse large-cell lymphoma in 1975 [29]. The CHOP regimen subsequently became standard treatment for patients with aggressive lymphomas and is also frequently used by clinicians to treat indolent lymphomas [5]. However, the standard CHOP regimen has not been proven to be capable of eradicating MRD in patients with follicular lymphomas, as documented by the persistence of cells bearing the *bcl-2* gene rearrangement in blood and marrow. This observation has encouraged the investigation of cyclophosphamide in combination with newer agents, such as rituximab, fludarabine, and mitoxantrone, in patients with relapsed disease [26, 30].

**Mitoxantrone-Containing Combination Regimens**

Besides its activity as a single agent in the treatment of patients with follicular lymphomas, investigators have reported responses with mitoxantrone in combination with fludarabine, with or without dexamethasone, that appear better than those obtained with single-agent fludarabine in similar patient populations [5, 23]. Four clinical trials using combinations of mitoxantrone and fludarabine (FM) were reported recently (Table 2). In one, FM was administered alone [6], whereas the other three trials used concomitant or sequential administration of rituximab. Of these latter three, one included a randomized comparison of FM and CHOP followed by rituximab in selected patients in both arms [31]. In the remaining two trials, FM was also combined with either dexamethasone (FND) or cyclophosphamide (FCM) [8, 30].

**FM for Patients with Untreated Indolent Lymphomas**

Based on studies of FND that reported good response rates for patients with relapsed indolent lymphomas, investigators in the Southwest Oncology Group designed a study (SWOG 9501) to determine the efficacy of FM in patients with untreated advanced indolent lymphomas [6]. In that study of patients with stages III and stage IV disease, the primary end point was progression-free survival (PFS). In the study of relapsed lymphomas reported by McLaughlin et al. [23], FND was associated with the development of opportunistic infections, particularly *Pneumocystis carinii*, when trimethoprim-sulfamethoxazole was not routinely administered. For this reason, dexamethasone was excluded from the FND regimen in the SWOG study with the objective of minimizing the occurrence of opportunistic infections [6]. However, prophylaxis against *Pneumocystis carinii* was still administered in the SWOG study, thereby further minimizing the risk of this complication of therapy.

Seventy-eight eligible patients were enrolled in the study. Forty-four percent attained CRs and 50% had PRs. The median PFS was 32 months, and the estimated 4-year PFS rate was 38%. The median overall survival time had not been reached with 88% of the patients alive at 4 years. Molecular response rates were not studied. The FM regimen was generally well tolerated, with infrequent mild gastrointestinal toxicities being the predominant nonhematologic side effects. Reversible myelosuppression was the major toxicity, with grades 3 and 4 neutropenic episodes occurring in 27 patients. Although 10 patients had documented infections, including three episodes of Herpes zoster...
in patients who received 4–8 cycles of chemotherapy, no life-threatening or fatal opportunistic infections occurred.

Overall, the SWOG trial indicated that FM is an effective, well-tolerated regimen for the treatment of patients with advanced indolent lymphomas. Although cross-trial comparisons can be misleading, the PFS with this regimen was similar to those reported with prior anthracycline-based SWOG regimens. Because this trial did not include dexamethasone, it is not possible to determine whether the efficacy of the FND regimen is equivalent to that of the CHOP regimen. The estimated 4-year OS rate in this trial was somewhat better than those reported from previous SWOG trials, but this result could possibly be attributed to an effect of better salvage therapy.

**FM with or without Rituximab Versus CHOP with or without Rituximab as Front-Line Therapy for Patients with Advanced Follicular Lymphomas**

Italian investigators performed a study to compare the efficacies of the FM and CHOP chemotherapy regimens, as measured by clinical and molecular response rates [31]. In that study, selected patients received rituximab following chemotherapy in both arms. The choice of whether to administer rituximab was based on clinical and molecular restaging; patients who achieved both clinical and molecular CRs did not receive rituximab; patients who achieved a clinical CR without a molecular CR or a PR with or without a molecular CR were treated with sequential rituximab immunotherapy; nonresponding patients went off study. Patients received either FM or CHOP at conventional doses, but with cycles repeated every 21 days (Fig. 1). Patients did not receive prophylaxis for *Pneumocystis carinii* infection. The primary study end points were the clinical CR rates with each regimen; secondary end points included molecular response, comparison of outcomes with and without rituximab, and OS, relapse-free survival, and PFS rates [31].

The analysis included 140 patients. Of those patients, the overall clinical response (OR) rates for FM (96%) and CHOP (98%) were similar, but the rate of CR was higher in the FM arm (68% and 42% for FM and CHOP, respectively; *p* = .003). The rate of molecular response was also higher in the FM arm (47% versus 29%; *p* = .030). Forty-one patients in the FM arm and 54 in the CHOP arm received rituximab following six cycles of either regimen. After rituximab, the number of patients with the combination of clinical and molecular CRs was higher in the FM arm (71% versus 51%; *p* = .01). In the overall study population, rituximab treatment led to significantly higher clinical CR (86%
versus 57%) and combined clinical and molecular CR rates (61% versus 29%). The estimated survival rate for the entire study population at 3 years was 94%. Hematologic toxicities were manageable in both arms, with no cases of treatment-related death or infection. CHOP was associated with significantly higher rates of grade 3 and 4 nausea and vomiting, alopecia, peripheral neurologic toxicity, and constipation (Table 3).

The results of that trial support the superiority of the FM regimen over CHOP chemotherapy in terms of clinical and molecular response rates. Importantly, FM therapy appeared to be better tolerated than CHOP therapy. Whether these response rates will translate into meaningful improvements in clinical outcome remains unknown. With a median follow-up of 19 months, there were no differences in the PFS and OS rates, but longer follow-up is required to

**Table 3.** Toxicities observed in Italian Multicenter Trial of FM versus CHOP chemotherapy

<table>
<thead>
<tr>
<th>Grade 3–4 toxicity</th>
<th>FM (n = 72)</th>
<th>CHOP (n = 68)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>22</td>
<td>27</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>2</td>
<td>15</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>10</td>
<td>58</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Peripheral neurologic toxicity</td>
<td>0</td>
<td>18</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>22</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>32</td>
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</tbody>
</table>

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; FM = fludarabine and mitoxantrone; NS = not significant.

assess these end points meaningfully. In addition, the study was not powered to show a difference in PFS or OS. There was also a significant response benefit from the addition of rituximab treatment for patients with incomplete clinical and/or molecular responses. This response benefit mitigated, to a large degree, the superiority of FN initially compared with CHOP. In comparison with the SWOG 9501 trial, the CR rate following FM treatment in the Italian trial was considerably higher, possibly due to the relatively greater dose intensity of the 21-day cycle.

**FCM and FCM with Rituximab for Recurrent Indolent Lymphomas**

The German Low Grade Lymphoma Study Group performed a randomized trial comparing FCM plus rituximab (FCM+R) with FCM alone in the treatment of patients with relapsed or refractory follicular, lymphoplasmacytic, or mantle cell lymphomas. Since most patients had received CHOP chemotherapy as initial treatment, a fludarabine-containing regimen was chosen for salvage therapy. One hundred forty-seven patients received treatment, randomized to either FCM alone for four courses given every 28 days or FCM+R on day 1 of each cycle. Of the 126 evaluable patients, 52% had follicular lymphomas and 38% had mantle cell histology [30].

Sixty-one percent of patients receiving FCM alone achieved CRs (14%) or PRs (47%), compared with 82% (37% CR rate and 46% PR rate) for patients receiving FCM+R (p < .007). The PFS (p < .028) and OS (p < .002) rates were also significantly better for patients receiving FCM+R. While only a little more than one-third of the patients treated with the combined therapy achieved CRs, these results reflect the adverse prognostic impact of having failed combination chemotherapy and the inclusion of mantle cell histology. Although requiring confirmation in additional studies with larger numbers of patients, this was the first prospective randomized trial to demonstrate that combined immunochemotherapy in patients with relapsed follicular and mantle cell lymphomas is superior to chemotherapy alone, both in terms of response and survival rates.

**Thiotepa, Vincristine, Prednisone, and Mitoxantrone plus Rituximab for Marginal Zone Lymphoma**

Marginal zone lymphoma (MZL) is a small cell subtype of indolent lymphoma for which no standard therapy has been established. As previously discussed, mitoxantrone is associated with less cardiotoxicity and alopecia than doxorubicin. Thiotepa, likewise, does not induce alopecia and is not associated with the immunosuppressive properties of fludarabine. The combination of thiotepa, vincristine, prednisone, and mitoxantrone (TOP-M) has been shown to be useful in elderly patients with diffuse large cell lymphoma [32]. The TOP-M regimen, consisting of thiotepa (7.5 mg/m²), mitoxantrone (7.5 mg/m²), vincristine, and prednisone as per the CHOP regimen, and rituximab (375 mg/m²), all given on day 1 of a 21–28 day cycle (in accordance with resolution of cytopenias), was administered to 12 patients with disseminated MZL [33]. Four patients received TOP-M alone and eight received TOP-M plus rituximab. The doses of thiotepa and mitoxantrone were escalated by a total of 2.5 mg to a maximum of 20 mg/m² based on nadir blood counts. Four patients had stage III disease, eight had stage IV disease, four
had B symptoms, and four had elevated lactate dehydrogenase levels. Treatment was well tolerated, with only two episodes of hospitalization for fever. There was no cardiac toxicity. Eleven of 12 patients (92%) had clinical responses, with nine (75%) confirmed and unconfirmed CRs (CR/CRu) and two (17%) PRs. The median duration of response had not been reached with a range of 11–40 months of follow-up. Based on these preliminary findings, TOP-M with rituximab appears to be a well-tolerated and active regimen for disseminated MZL and may have utility for the treatment of other indolent lymphomas.

CONCLUSIONS AND FUTURE DIRECTIONS
Mitoxantrone-based regimens are highly active and well tolerated in the treatment of patients with both relapsed and previously untreated indolent lymphomas. The Italian multicenter trial was the first randomized comparison of a fludarabine-based regimen with standard CHOP chemotherapy. In that trial, compared with CHOP, FM was associated with significantly higher clinical and molecular response rates and significantly better tolerability. Despite the superior clinical and molecular response rates, the FFS and OS rates were not better with FM therapy, possibly in part related to the treatment design of the study. The relatively small numbers of patients and short duration of median follow-up also made it difficult to interpret these survival data definitively. However, in other studies, investigators have found a significantly longer FFS in patients who achieve molecular responses within the first year of treatment, compared with those who still have positive molecular findings [11]. The addition of rituximab appears to increase the activity of FM regimens in patients with indolent NHL [31]. In the Italian multicenter trial, the sequential administration of rituximab produced higher clinical and molecular response rates in patients treated with FM. In the study of FND plus concurrent or sequential rituximab performed at the MD Anderson Cancer Center, concurrent FND+R resulted in a slightly higher 3-year FFS than sequential FND+R; these results were significantly better for the follicular lymphoma subset [8]. In the German Low Grade Lymphoma Study Group trial, combination chemoimmunotherapy with FCM+R was superior to FCM alone in terms of response, PFS, and OS rates [30]. To date, that trial provides the only direct comparative evidence supporting the addition of rituximab to mitoxantrone-based therapy for relapsed disease. Although chemotherapy and immunotherapy exert antitumor effects through different mechanisms of action, with generally nonoverlapping toxicities, additional research is needed to confirm the benefit of combined chemoimmunotherapy and to define optimal dosing schedules. The combination of these modalities offers an attractive approach to improving overall clinical outcomes in patients with low-grade lymphomas.

Mitoxantrone is associated with few significant grade 3–4 nonhematologic side effects. Because mitoxantrone has a lower cardiotoxic potential than doxorubicin, it may be advantageous to initially use mitoxantrone in the treatment of patients with indolent NHL, reserving doxorubicin for later use. However, this hypothesis has yet to be clinically tested. Mitoxantrone-based regimens can also be offered to patients who are concerned about anthracycline-associated alopecia. Central venous access is not required for the administration of mitoxantrone in any combination, since extravasation of this drug does not produce significant tissue injury or necrosis. Mitoxantrone also appears to be associated with less gastrointestinal toxicities than CHOP, including nausea and vomiting, abdominal pain, and constipation, making it an attractive drug to use in combination with fludarabine as therapy for older patients.

Because FM-based regimens use only 3 days of treatment with fludarabine, in contrast to 5 days with other fludarabine-containing regimens, FM may also be a preferable choice for patients who subsequently undergo autologous or allogeneic stem cell transplants. The primary toxicity of fludarabine is myelosuppression, which may be prolonged in some patients, especially in those receiving higher doses or prolonged therapy [19–21]. Given the greater potential for serious myelotoxicity associated with greater fludarabine exposure, a shorter 3-day course may be a safer alternative when given in combination with mitoxantrone.

A potential new approach is the sequential combination of chemotherapy with radioimmunotherapeutic agents, such as the anti-CD20 radioimmunoconjugates 131I-tositumomab and 90Ytrium-ibritumomab-tiuxetan. Both agents have demonstrated activity in patients with follicular lymphomas refractory to both prior chemotherapy and rituximab [34-37]. New studies combining mitoxantrone-containing regimens with radioimmunoconjugates are planned and may add to our knowledge of the benefit of these drugs.

Despite therapeutic progress, cure remains the ultimate goal for patients with indolent lymphomas. Whether this can be achieved now is conjectural; however, prolongation of life, enhanced quality of life with PFS, and minimizing toxicity are goals equally important and hopefully achievable.

Brief Patient Case
A 56-year-old female executive of a high fashion magazine fortuitously noticed a 2.5-cm left supraclavicular node while dressing. Her history includes rheumatic fever and murmur as a child as well as smoking 1–2 packs of cigarettes per day for 30 years. A computed axial tomography (CAT) scan disclosed hilar lymphadenopathy but clear lung fields and she was asymptomatic. A node biopsy established the diagnosis of follicular, grade one lymphoma.
Work-up revealed 1–2 cm nodes in the inguinal area, but all laboratory data were otherwise unrevealing. The patient emphasized that she must maintain her appearance and hectic pace for the next several years and was managed with observation. After 1.5 years, she presented with a history of rapidly growing peripheral nodes and weight loss. Evaluation disclosed no evidence of transformation; however, a CAT scan showed significant abdominal lymphadenopathy with some impingement on the ureters and moderate bilateral hydronephrosis. There was also a 20-cm enlarged spleen with some pressure effects on the stomach. Cardiac evaluation showed a multigated acquisition (MUGA) scan ejection fraction of 55%. Creatinine clearance was 55 ml/minute. The patient was treated with FM+R in order to achieve a rapid response. She had an excellent response, remained in response for 20 months, and was able to maintain her current lifestyle during and after treatment.

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