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TREATMENT OF INDOLENT LYMPHOMA WITH FLUDARABINE/MITOXANTRONE COMBINATION: A PHASE II TRIAL

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SUMMARY

In an effort to reduce the risk of opportunistic infections, 25 patients with advanced indolent lymphoma (age range: 30–77 years) were treated, using a combination of fludarabine and mitoxantrone, without corticosteroids. Fludarabine was given at 25 mg/m^2 for three daily doses, and mitoxantrone at 10 mg/m^2. Cycles were repeated every four weeks for up to maximum response, and for no more than six months. Eight patients had follicular lymphoma, and 11 had CLL/SLL. Objective response was observed in 11 of 12 previously untreated patients, including five complete remissions, and in 10 of 13 previously treated patients, including three complete remissions. Only two relapsed patients failed to respond, whereas two patients were not evaluable. Hence, the overall response rate based on the intention-to-treat analysis was 84 per cent (95 per cent CI: 70–98 per cent). The median survival has not been reached after a 22-month follow-up. Median time to progression was 15 months. One patient on corticosteroids developed pneumocystis carinii pneumonia, and an elderly patient succumbed to neutropenic sepsis. Apart from granulocytopenia, the treatment was well tolerated. Omission of corticosteroids reduces the risk of opportunistic infections, while the activity of the combination against indolent lymphoma and CLL is maintained.

KEY WORDS fludarabine; mitoxantrone; lymphoma, indolent, follicular, small lymphocytic; chronic lymphocytic leukemia; GMCSF; pneumocysti carinii pneumonia

INTRODUCTION

Indolent lymphomas are usually incurable malignancies that can be transiently controlled with chemotherapy. Optimal treatment should combine efficacy with tolerability and should produce durable responses. The introduction of nucleoside analogues has enriched available chemotherapy options in the management of lymphomas. Fludarabine, an adenosine deaminase resistant adenosine analogue, has already been widely accepted as an effective agent in the treatment of low-grade lymphoma, Waldenstrom's disease and chronic lymphocytic leukemia. Response rates of 41–80 per cent in previously untreated patients with low-grade lymphoma (LGL) or chronic lymphocytic leukemia (CLL) have been reported.[1,2,3,4] Very good response rates of 31–68 per cent have also been noted in relapsed or refractory patients.[5,6,7,8] In addition to inhibition of DNA synthesis which may affect rapidly proliferating cells, fludarabine has a remarkable activity against resting lymphocytes, causing apoptosis, presumably due to RNA

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inhibition or possibly NAD depletion.[9,10] These results indicate that fludarabine is one of the most useful agents against indolent lymphoid malignancies.

Mitoxantrone is an anthracenedione that was discovered in the search for less toxic doxorubicin analogues, and has a well documented activity in lymphoid malignancies.[11,12] In a large study involving 206 patients with relapsed non-Hodgkin's lymphona (NHL) and Hodgkin's disease, most of which had had prior treatment with anthracycline, monotherapy with mitoxantrone produced a 37 per cent response rate with a median duration of response of 323 days in patients with NHL. Similarly to doxorubicin, mitoxantrone may act in synergy with other antineoplastic agents, including nucleoside analogues.[13] Various mitoxantrone-containing combination chemotherapy regimens are used for the treatment of lymphocytic malignancies.

The combination of fludarabine with mitoxantrone and dexamethazone (FND) has been pioneered by Mclaughlin *et al.* at the M. D. Anderson Cancer Center and has been shown to be an effective regimen for indolent lymphoma.[14] However, the combination was found to be very immunosuppressive. The observed significant risk of opportunistic infections necessitated the use of infectious prophylaxis. Since it appears that combining corticosteroids with fludarabine may result in marked immunosuppression, in the current study corticosteroids were omitted in an effort to reduce treatment-related morbidity. The toxicity and efficacy of the fludarabine–mitoxantrone regimen, without co-administration of corticosteroids, is hereby presented.

METHODS AND RESULTS

Patients selection

Between August 1994 and October 1996, 25 adult patients with previously untreated, refractory or relapsed indolent lymphoid malignancies participated in the study. Patients needed to have adequate performance status (ECOG 0–2), adequate marrow function (granulocyte count >500 per μl, platelets >50 000 per μl), renal function (serum creatinine <2 mg per cent), liver function (direct bilirubin <2 mg per cent) and cardiac function (left ventricular ejection fraction >50 per cent). Patients who had previously received fludarabine or mitoxantrone were excluded. Patients were treated after signing an informed consent form approved by the institutional review board.

In addition to routine blood tests, staging evaluation included CT scans of the chest, abdomen and pelvis or other imaging of involved areas; pre-treatment bone marrow aspiration and biopsy, and CD4 counts of the peripheral blood were obtained.

Treatment plan

Fludarabine was administered at a dose of 25 mg/m^2 daily for three consecutive days, and mitoxantrone was given at 10 mg/m^2 on the first day of the treatment cycle. Cycles were repeated every four weeks up to maximum response and for no more than six cycles. All patients were premedicated with anti-emetics.

A blood count was obtained weekly during treatment, and a chemistry panel was obtained prior to each cycle. Chemotherapy was withheld if the granulocyte count had not reached 1000 per μl and the platelet count 50 000 per μl. If the ANC nadir fell below 500 per μl (grade 4 granulocytopenia) or a cycle had to be delayed for incomplete granulocytic recovery, sargramostin (GMCSF) 500 μg sc daily for ten days starting on the first post-treatment day was administered, for all subsequent cycles.

Table 1. Patient characteristics

Age in years, median/range:	61 (30–77)
Female	8
Male	17
Previously untreated	12
Relapsed or refractory	13
Stage IV, or Rai >2	24
Bulky disease, >8 cm or spleen >20 cm	9
Histology:	
SLL/CLL	11
Follicular	8
Lymphoplasmacytoid	2
Maltoma	2
Mantle cell	1
T-cell	1

If grade 4 neutropenia recurred despite the use of sargramostin, both chemotherapy drugs were reduced by half. Patients were withdrawn from the study if their counts had not recovered by the sixth week post-treatment.

Response was assessed after the second, fourth and last cycle by radiological imaging and by bone marrow examination if initially involved. Complete response (CR) was defined as the disappearance of lymphadenopathy (<1 cm), and negative histological examination of bone marrow or peripheral blood. Negative histology with detection of minimal residual disease revealed only by flow-cytometry analysis, or presence of scarce lymphocytic aggregates inconclusive for malignancy, were allowed in the definition of CR.[15] Partial response (PR) was defined as a more than 50 per cent reduction of the sum of the products of diameters of all the measured lesions and a more than 50 per cent reduction of extent of bone marrow involvement. Any response less than PR was considered treatment failure. Peripheral blood CD4 counts were obtained after the fourth cycle and again 4–6 months after the end of treatment. Patients were considered evaluable for response if they had received at least two cycles.

Statistics

Fisher's exact test was used for comparison of proportions between groups.

Patients characteristics

The characteristics of the 25 patients of this study are shown in Table 1. Seven patients were more than 65 years old, with an upper age of 77 years. The histological subtypes of the treated patients are also shown in Table 1. A patient with mantle cell lymphoma was included because of 'indolent' appearing histology. Of the 13 previously treated patients, nine had relapsed between four months to three years following alkylator-based treatment; four patients had received anthracycline-containing combination chemotherapy. Two patients had progressing disease while on treatment, whereas two patients were previously treated only with involved field irradiation. The median time since diagnosis for the relapsed patients was three years (range: 0·5–12 years).

All lymphoma patients had stage IV disease (Ann-Arbor); all but one of the CLL patients had Rai III or IV disease. Bulky

Table 2. Treatment delivery

	CLL/SLL	All patients
Total no. of cycles	53	106
Average no. of cycles per patient	4·2	4·2
Dose intensity (actual/planned)	0·78	0·79

Table 3. Response by intention to treat

	Previously untreated (n=12)	Previously treated (n=13)	All patients (n=25)
Overall response	11	10	21 (84%)
Complete response	5	3	8 (32%)
Partial response	6	7	13 (52%)
Progression	0	2	2 (8%)
Withdrawal after first cycle	1	1	2 (8%)

disease was defined by the presence of a nodal mass of at least 8 cm (seven patients) or spleen size more than 20 cm in the largest dimension (two patients).

Response

An average of 4·2 cycles per patient were given (range 1–6, median 5 cycles). Two patients were withdrawn from the study because of prolonged cytopenia after the first cycle; a heavily pre-treated patient with follicular lymphoma (10 cycles of CHOP) developed prolonged granulocytopenia, and another patient with extensive and untreated mantle cell lymphoma as well as borderline thrombocytopenia prior to treatment did not reach a platelet count of 50 000 by the sixth week after the first cycle.

Based on the intention-to-treat analysis (25 patients), a 32 per cent CR rate and a 52 per cent PR rate was noted to give an overall response rate of 84 per cent (95 per cent CI: 70–98 per cent). Twenty-one out of the 23 patients who completed the treatment responded; 8 had complete responses and 13 had partial responses (Tables 2 and 3).

All previously untreated patients who completed treatment responded; five achieved a complete response and six a partial response. Hence, based on intention to treat, the response rate was 91 per cent (CI: 77–100 per cent). Ten out of 12 previously treated patients who completed treatment responded; three patients had a complete response and seven a partial response. Based on intention to treat, previously treated patients had an overall response of 77 per cent (CI: 55–99 per cent). Response rates favoured previously untreated patients compared with relapsed patients, but the differences did not reach statistical significance (p=0·26). Good responses were noted in patients with a high tumour burden; out of nine patients with bulky disease as defined above, two achieved a CR, six had a PR and one failed (Table 4). Complete response was noted in one out of seven evaluable patients with follicular lymphoma, and in six out of 11 patients with SLL/CLL (p=0·07).

Table 4. Response according to subset

Subset	CR	PR	No response
By histology:			
A. SLL/CLL – de novo ($n=5$)	3	2	–
B. SLL/CLL – progressive/relapsed ($n=6$)	3	2	1
SLL/CLL – all evaluable patients ($n=11$)	6	4	1
Follicular ($n=7$)	1	6	–
Other ($n=5$)	1 (plasmacytoid)	3 (maltoma × 2, T-cell)	1 (plasmacytoid)
By tumour burden:			
Mass >8 cm ($n=9$) or spleen >20 cm	2	6	1

One patient with extensively treated bulky lymphoplasmacytoid lymphoma, and a patient with CLL that had failed CHOP, showed no response after the second cycle of treatment and were considered treatment failures.

The median freedom from progression time (FFP) for the 23 patients who completed treatment and were evaluable for response was 19 months. Out of the 21 responders, 5 patients remained in clinical remission to 22, 26, 28, 32 and 37 months, whereas 16 patients have progressed. One patient with follicular lymphoma who had a partial response transformed to aggressive histology soon after the end of the treatment. Another two patients underwent high-dose chemotherapy followed by BMT while in stable PR and have relapsed since. Relapses have occurred in 13 of the remaining 18 patients who were followed expectantly post-treatment. One patient with CLL suffered a central nervous system relapse 32 months after treatment. Four patients who relapsed at 23, 25, 30 and 30 months, and to date have been followed between 3–9 months after relapse, have not required treatment for their asymptomatic, slowly progressive disease. Of the eight patients who achieved CR, four have relapsed at 30, 25, 30 and 30 months since the beginning of treatment, whereas four remain in CR at 22, 26, 32 and 37 months.

The median FFP for patients with follicular lymphoma was 15 months, whereas FFP for CLL/SLL patients was 28 months ($p=0{\cdot}04$). The median survival of the whole group has not been reached after a median follow-up of 37 months. The following ten patients have died: two patients who withdrew due to low blood counts; a patients whose lymphoma transformed; two patients who progressed while on treatment; two patients after BMT (one allogeneic, one autologous) who achieved a PR; two patients with bulky disease who had achieved a PR; and a patient who succumbed to neutropenic sepsis.

Toxicity

In general, the combination was tolerated well. The 25 patients received a total of 106 cycles (average 4·2 cycles per patients, median 5 cycles). The fraction of the intended dose intensity that was delivered was 0·79.

The main toxicity consisted primarily of myelosuppression and secondarily of infections. Non-hematological toxicities were uncommon and clinically insignificant (<grade 2). One hundred cycles were evaluable for hematological toxicity. Grade IV neutropenia occurred in 37 (95 per cent CI: 28–46 per cent); grade III neutropenia occurred in an additional 40 cycles (CI: 31–49 per cent). Twenty of the 25 patients (80 per cent) developed grade IV granulocytopenia at some point during the treatment, and 18 of them received GMCSF. Overall, 42 cycles

(42 per cent) were supported by GMCSF. Among the previously untreated patients, grade IV granulocytopenia after the first cycle occurred only in the two patients who were over 70 years old, but in none of the remaining 11 patients under 70 years of age ($p<0{\cdot}05$).

Thrombocytopenia grade III (platelet count between 20 000–50 000 per mm^3) occurred in two patients. No patient required platelet or red cell transfusion. Delay of administration due to myelosuppression occurred in seven patients, and dose reduction was required in five patients.

Two patients were withdrawn from the study because of myelotoxicity. One patient who had received ten cycles of CHOP for her follicular lymphoma had prolonged granulocytopenia lasting for longer than six weeks after the first cycle of treatment. Another patient with mantle cell lymphoma had a borderline platelet count prior to the treatment, and did not recover over 50 000 per mm^3 within six weeks of the first cycle. A treatment-related death occurred in a 77-year-old man with peripheral T-cell lymphoma after the fifth cycle of treatment. The patient had already achieved a partial response and received a dose-modified cycle with GMCSF support due to previous cytopenia. Despite these precautions, his pancytopenia persisted and he eventually succumbed to sepsis eight weeks after the last cycle. After this adverse event, the protocol was modified so that patients over 70 years old did not receive more than four cycles of treatment.

Uncomplicated neutropenic infections occurred in four instances, including a patient with bacterial pneumonia readily responding to intravenous cephalosporine treatment, and one patient with catheter-related sepsis. One patient developed herpes zoster four months after completion of treatment while in partial response. An episode of uncomplicated C. difficile-associated diarrhoea was noted. One episode of pneumocystis carini pneumonia (PCP) occurred in a patient who had been on a long course of corticosteroids (60–100 mg daily for over two months) for severe auto-immune hemolysis occurring prior to and during the first cycles of the treatment. At the time of the diagnosis of PCP his steroid dosage had been tapered to 30 mg of prednisone daily. After treatment of PCP he was able to complete chemotherapy with PCP prophylaxis; his hemolysis resolved off corticosteroids and he is in a stable remission.

During treatment, the CD4 count was reduced (range 50–722 per μl, median 220), as expected by the leukopenia induced by the regimen. The CD4 count remained suppressed during the immediate period of 2–5 months after completion of treatment, with a range of 148–647 per μl (median 179).

DISCUSSION

In the present study, the combination of fludarabine and mitoxantrone is shown to be effective in the management of low-grade lymphoma. This study included patients with a variety of indolent lymphoid malignancies, including small lymphocytic lymphoma/chronic lymphocytic leukemia, follicular lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma (Waldenstrom's disease). A significant proportion of the patients had large tumour bulk and some had heavy previous treatment. The efficacy of the combination was demonstrated for most types of indolent lymphomas. All of the evaluable, previously untreated patients responded. Very good results were also observed in relapsed or refractory patients, with only two of the evaluable patients failing to respond. These findings suggest that the combination has a satisfactory efficacy in fludarabine-naive patients with indolent lymphoma.

Mitoxantrone is an anthracendione, an agent related to doxorubicin, with favourable tolerability and less than 5 per cent incidence of cardiotoxicity.[16,17] It is generally effective against myeloid and lymphocytic hematological malignancies. Its efficacy in relapsed lymphoma

have been demonstrated in large cooperative group studies.[12,18,19] In these studies, mitoxantrone monotherapy resulted in responses ranging between 25–37 per cent regardless of previous anthracycline treatment. Excellent single agent activity with modest toxicity has been reported in patients with low-grade lymphoma.[11] These clinical results are supported by the observation that mitoxantrone can induce apoptosis in CLL cells *in vitro*.[20] Because of the observed efficacy, relative lack of cardiotoxicity, and possible synergistic action with other agents,[13] mitoxantrone has been included in combination treatments for lymphoma, with other agents such as etoposide, ifosfamide (MINE),[21] and prednimustine.[22]

Previous studies have documented the efficacy of fludarabine in lymphoid malignancies. Fludarabine can produce an 80 per cent response rate in untreated patients with CLL and a 60–70 per cent response rate in patients with indolent lymphoma.[1,4,23, 24] Remarkable response rates in the range of 40–50 per cent have been observed in relapsed or refractory patients.[25,26] Combinations with corticosteroids have also been tested extensively, although this addition has not been clearly shown to improve response rates.[27,28] Obviously, direct comparisons with these studies cannot be made because of differences in patient populations, definitions of response, and other confounding factors. However, the observed overall response rate of 84 per cent in our group of patients, as well as results of others testing fludarabine–mitoxantrone based treatments, as described below, compare favourably with the fludarabine monotherapy outcome and may suggest an advantage to using the combination of the two drugs. This is supported by *in vitro* data showing synergy of the two agents against CLL cells obtained from patients.[20]

Several publications have already described results using a fludarabine–mitoxantrone–corticosteroid combination. In a study of fludarabine–mitoxantrone given with 40 mg of prednisone for five days each cycle, a 72 per cent response rate among 18 patients with relapsed lymphoma was reported.[29] In a larger study of similar doses of fludarabine and mitoxantrone co-administered with 20 mg of dexamethasone for five days (FND) to 51 patients with recurrent or refractory indolent lymphoma, the MD Anderson Group reported a 94 per cent response rate.[14] The combination of the two drugs used at the same dose produced a 77 per cent response in our relapsed lymphoma patients (CI: 55–99 per cent). Again, direct comparison of the results of these studies cannot be done. Possibly, the inclusion of potent corticosteroids such as dexamethazone in the regimen may slightly enhance efficacy. However, the potential advantage of adding corticosteroids should be weighed against augmentation of the risk for treatment-related infectious complications. In the above-mentioned study of FND, six patients were reported to develop PCP. This observation led the investigators to institute prophylaxis for subsequently enrolled patients. In our cohort, despite the fact that PCP prophylaxis was not given, only one patient who was receiving prednisone for control of pre-existing hemolytic anemia developed PCP.

The association between the development of opportunistic infections and treatment with the fludarabine–corticosteroid combination seems to be emerging from several published reports. In the MD Anderson study of FND, 13 episodes overall of opportunistic infections were noted. A previous retrospective analysis by Anaissie *et al*. described the development of opportunistic infection by listeria in 1·7 per cent of CLL patients treated with fludarabine and prednisone, while none of the 160 patients who received fludarabine alone developed listeriosis.[30] It is known that fludarabine treatment induces a prolonged quantitative defect of CD4 lymphocytes, with an average number below 200 per μl at the end of treatment and a slow, gradual recovery for up to one year thereafter.[31] The above observations suggest that immunosuppression caused by fludarabine tends to become clinically significant mainly when there is exposure to corticosteroids. Interestingly, the use of corticosteroids does not need to be concurrent with fludarabine for

the development of infections.In another report, prednisone treatment could have preceded or followed fludarabine administration in patients who were diagnosed with opportunistic infections.[27] Again, opportunistic infections were not observed in patients who did not receive corticosteroids. It appears that fludarabine-induced reduction of the CD4 T-lymphocytes lowers the threshold to opportunistic infections which occur with the combined action of other immunosuppressive agents, such as corticosteroids. This would explain our finding of the development of PCP only in a patient who was getting corticosteroids simultaneously, and for the incident of herpes zoster four months after completion of treatment in a patient receiving dexamethazone for his progressive lymphoma. Consequently, patients who are not receiving or have not received corticosteroids in temporal proximity with fludarabine may not be at significantly higher risk of opportunistic infections and may be spared the side-effects of prophylaxis.

Except for neutropenia, the combination was well tolerated, causing minimal morbidity overall. The main toxicity was myelosuppression which was extreme in a few instances. Grade III or IV granulocytopenia occurred in the majority of the cycles. Cumulative myelosuppression seemed to occur in some patients, and was especially apparent in the case of the elderly man who died from neutropenic sepsis after the fifth cycle. Relative renal dysfunction is often under-diagnosed in the elderly, if the serum creatinine value is used as the sole renal index. Since blood fludarabine levels show a close and inverse correlation with creatinine clearance, it is possible that elderly patients are relatively overdosed.[32] Dose reduction up-front, and treatment for as few cycles as possible, may be a safer way to administer fludarabine–based treatment in the elderly. The administration of sargramostin was effective in shortening the duration and occasionally the depth of neutropenia. Interestingly, no infection or febrile episode occurred in patients while on sargramostin; although not in the scope of this study, this observation alludes to a protective effect of sargramostin against infections, possibly independent of the extent of neutropenia.[33]

In our group of patients, several had large lymphomatous masses. Encouraging results were observed in these patients, especially as those with bulky disease are usually destined to do worse. Among our group of patients, several long-term remissions have been noted. Persistence of remissions at 20, 26, 28 and 37 months have been noted in four patients with SLL/CLL; a patient with lymphoplasmacytoid lymphoma is in remission at 32 months. The preferentially exceptional activity against CLL/SLL and the effectiveness of fludarabine-based treatment in a variety of types of indolent lymphoma as well as the remarkable durability of the remissions in a subgroup of patients with non-follicular indolent lymphoma or CLL are in agreement with previous reports.[34,35] It remains unclear why fludarabine-based treatments seem to be particularly effective in CLL/SLL patients.

In conclusion, the combination of fludarabine and mitoxantrone is an effective and tolerable regimen that can be used as initial or salvage treatment in fludarabine-naive patients with a variety of indolent lymphomas. The combination seems to be more potent against SLL/CLL. Dose modification and reduction of number of cycles administered may be required for elderly patients. The immunosuppressive effects of the combination are moderate and clinically inapparent. However, the use of corticosteroids during or after treatment possibly exposes patients to a considerable risk of opportunistic infections, whereas it remains unclear whether efficacy is enhanced.

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