Phase II study of fludarabine and α-interferon in patients with low-grade non-Hodgkin's lymphoma

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A B S T R A C T

Background and Objectives. Low-grade non-Hodgkin's lymphoma (NHL) remains incurable with standard dose chemotherapy. Nucleoside analogs such as fludarabine are effective, but even when used as initial therapy, the median duration of remission ranges from only 16 to 24 months. Interferon (IFN) is also active and has been investigated both by incorporating it into the chemotherapy regimen and/or as maintenance therapy, where it may prolong remission. We designed a phase II trial of alternating fludarabine and IFNα2a to determine response rate, time to progression and toxicity of this regimen in patients with advanced stage low-grade NHL or mantle cell lymphoma.

Design and Methods. Patients had received 0-2 prior regimens that did not include nucleoside analogs or IFN and had adequate organ function. Fludarabine was administered intravenously at 25 mg/m^2/day for 5 days once every 6 weeks with IFN in weeks 4 and 5 at 3×10^6 U/m^2 subcutaneously three times weekly for 6 doses. Treatment continued in responders for 2 cycles past maximal response (minimum 6 cycles). No maintenance was given.

Results. Between 1994 and 1999, 31 patients were accrued and were evaluable for toxicity, with 29 eligible for evaluation of response. Toxicity was primarily myelosuppression, with grade 3 neutropenia in 12 patients and grade 4 thrombocytopenia in one patient. The overall response rate was 51.7% (15/29), including 6 complete and 9 partial responses. With a median follow-up of 35.6 months, the median overall survival was 60.8 months, and the median time to disease progression (TTP) was 12.6 months. Of the 15 responding patients, treatment-naïve patients had a median response duration of 39.6 months with a median TTP of 42.1 months, while the median response duration was 5.2 months with a median TTP of 14.5 months in patients who had received prior treatment (p=0.0065 and 0.0374, respectively).

Interpretation and Conclusions. This schedule of alternating fludarabine with IFN does not seem to increase response rate appreciably, but there are some prolonged responses, particularly in previously untreated patients. Given the non-overlapping toxicities of IFN with those of chemotherapy and antibody-based therapeutics, there may be a role for combination therapies, especially if the biological basis of response to IFN can be elucidated.

Key words: fludarabine, α-interferon, low-grade NHL.

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Low-grade non-Hodgkin's lymphomas (LG-NHL) as well as mantle cell lymphomas are highly responsive to chemotherapy yet are considered incurable with standard chemotherapy.[1,2] In LG-NHL, the nucleoside analog fludarabine produces responses in 50-60% of patients,[3-10] with a median duration of response reported to be approximately 16 to 24 months.[1,11,12] The response rate is even higher in previously untreated patients.[10,12,13] However, despite the high response rate to nucleoside analogs, these drugs are not curative.[3-7,14,15] Interferon α (IFN) has activity in a spectrum of diseases, including LG-NHL,[16,17] for which it is approved for use in the United States. Since IFN appears to be more effective in cases with low tumor burden, it has been evaluated as maintenance therapy, for instance in myeloma.[18] Another approach is to combine IFN with chemotherapy,[19,20] often concurrently; however, this may be antagonistic if IFN works by a cytostatic mechanism, and toxicity of the combination therapy may limit chemotherapy doses. In contrast, alternating chemotherapy with IFN in theory allows potentially non-cross-resistant agents to be given while avoiding additive toxicities. Pilot studies in multiple myeloma as well as a recent phase III study in patients with refractory disease showed increased complete remission (CR) rates when patients were treated with IFN added to chemotherapy.[21,22] A subsequent ECOG phase III study reported by Oken *et al.* also showed that duration of response was longer in those patients treated with the combination of IFN and chemotherapy than in those treated with chemotherapy alone.[23] Based on these intriguing data, we elected to study fludarabine combined at full doses with a course of IFN in an alternating

schedule analogous to that used for myeloma to determine whether this type of schedule would increase the efficacy of therapy in LG-NHL. We included mantle cell lymphoma patients eligible for treatment as, even now a decade after this protocol began, this disease remains incurable with current therapy, and the optimal therapy for this subset of patients is still unclear.

Design and Methods

Patients' eligibility

At the time this protocol was written, patients' eligibility was defined by the International Working Formulation (IWF) and retrospectively according to their corresponding WHO classification. Patients were deemed eligible for the protocol if they had a biopsy-confirmed diagnosis of low grade non-Hodgkin's lymphoma including small lymphocytic malignant lymphoma (ML) not meeting criteria for chronic lymphocytic leukemia (CLL) (IWF class A); follicular predominantly small cleaved cell ML (IWF class B); follicular mixed small cleaved and large cell ML (IWF class C); intermediate differentiation or mantle zone lymphoma; and mucosa-associated lymphoid tissue lymphoma (MALT-oma). The current WHO classification describes these cell types as mature B-cell neoplasms, and they were chosen because of their incurable nature. Lymph node and bone marrow pathology was reviewed at Fox Chase Cancer Center as well as affiliated Fox Chase Cancer Center Networks. Eligible patients were aged 18 years or older, had ECOG performance status 0-2 and bidimensionally measurable Ann Arbor stage III or IV disease, or stage II if not a candidate for definitive radiation therapy, and had received a maximum of 2 prior chemotherapy regimens with no prior nucleoside analog or interferon. No concomitant corticosteroids were permitted. Prior radiation was allowed if it had not encompassed the entire pelvis and if evaluable disease remained outside the radiation port. Neutrophil counts had to be ≥2000/μL and platelets ≥100,000/μL, unless considered to be due to bone marrow involvement. Patients had to have adequate renal function with creatinine less than twice the upper limit of the laboratory's normal values and adequate liver function with serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin less than twice the upper limit of the laboratory norm. Women of child-bearing potential had to have had a negative pregnancy test, agreed to use effective contraceptive methods, and could not breast-feed while on study. All patients signed IRB-approved informed consent. Given the inclusion of interferon in the treatment schema, the study excluded patients with active infection requiring antibiotic therapy; unstable angina or uncontrolled congestive heart failure; severely debilitating pulmonary disease; a history of diabetes mellitus prone to ketoacidosis; any active coagulation disorder, such as thrombophlebitis or pulmonary embolism; a prior history of severe psychiatric disorder; a history of autoimmune hepatitis; pre-existing thyroid disorder with thyroid function unable to be maintained in the normal range; clinical evidence of central nervous system involvement with lymphoma; other malignancy within the last 5 years except non-melanoma skin cancer or carcinoma *in situ*.

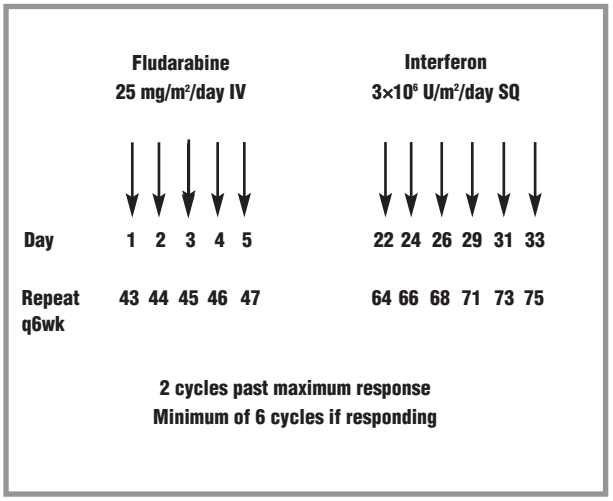

Figure 1. Fludarabine/interferon treatment scheme. See Design and Methods section for details.

Treatment plan

The treatment schema is outlined in Figure 1. Fludarabine, obtained commercially, was administered intravenously at a dose of 25 mg/m²/day on days 1-5 of each cycle. No routine steroids were permitted as antiemetics, and antiemetic therapy was otherwise as prescribed by the treating physician. Interferonα-2a (Roferon, generously supplied by Roche, NJ, USA) was administered subcutaneously at a dose of 3×10^6 U/m² (adjusted to the nearest 0.5×10^6 U) three times weekly for six doses beginning on day 22 of each cycle, if blood counts were adequate. Cycles were repeated every 42 days, with at least five days between the last IFN injection and the beginning of the next cycle. Treatment continued for two cycles after maximum response, and a minimum of six cycles for responding patients.

Evaluation while on treatment consisted of measurements of complete blood count (CBC), creatinine, and blood urea nitrogen (BUN) on day 15 and CBC on day 22 and day 36 of each cycle, or weekly thereafter if IFN therapy was delayed. Physical assessment for tumor measurements and toxicity was performed on

the first day of each cycle. CBC with differential, chemistry panel and, if initially abnormal, erythrocyte sedimentation rate (ESR) and serum protein electrophoresis/ immune electrophoresis (SPEP/IEP), were performed on or within 8 days prior to the first day of each cycle. Radiological assessment of response (chest X-ray and/or CT/MR of involved areas) was performed after every second cycle. Bone marrow examination and cytogenetic testing were repeated at the end of therapy in responders with initial bone marrow involvement. Post-treatment follow-up was performed every two months until disease progression or death.

Dose modifications

Dose delay. Fludarabine and/or IFN doses were delayed if neutrophil counts were ≤2000/μL or platelets ≤75,000/μL, and held until these criteria were met. Bone marrow was re-examined for involvement with lymphoma if cytopenias persisted beyond three weeks. If there was no resolution after an additional three weeks, patients were taken off study. Myeloid growth factors were considered at the discretion of the treating physician, only after neutropenia had developed with the patients taken off study if febrile neutropenia recurred.

Dose reduction. The dose of fludarabine was reduced to 18 mg/m^2/day in patients who developed neutropenic fever or documented infection despite administration of hematopoietic growth factors. The dose of IFN was reduced by 50% for patients with intolerable side effects of IFN, including constitutional symptoms refractory to the administration of acetaminophen and/or anti-inflammatory medication, and further reduced to twice weekly if symptoms persisted.

Response criteria

Responses were defined according to standard Eastern Cooperative Oncology Group criteria at the time the protocol was written. Complete remission (CR) was defined as the following for a minimum of 4 weeks: absence of lymphadenopathy, hepatomegaly or splenomegaly, absence of constitutional symptoms, normal CBC and normal marrow. Partial remission (PR) was defined as a ≥50% reduction in the size of bidimensionally measurable disease, neutrophils ≥1500/μL, platelets ≥100,000/μL, and hemoglobin ≥11.0 g/dL or ≥50% improvement over baseline(s) without transfusions. Patients with leukemic phase LG-NHL had to have a ≥50% decrease in peripheral blood lymphocyte count from the pretreatment value. Progressive disease (PD) was defined as at least one of: ≥25% increase in the bidimensional product of at least two lymph nodes on two consecutive examinations at least two weeks apart; appearance of new lymphadenopathy; ≥25% increase in the size of the liver and/or spleen as determined by measurement below the costal margin or appearance of new palpable hepatomegaly or splenomegaly; or ≥50% increase in absolute number of circulating lymphoma cells to an absolute number >15,000/μL. Stable disease (SD) was defined as cases which did not meet the criteria for CR, PR or PD.

Toxicity assessment

Non-hematologic toxicity was graded according to NCI common toxicity criteria (version 2.0). For patients without initial bone marrow compromise, hematologic toxicity was also graded by NCI common toxicity criteria. For patients with initial bone marrow compromise, defined as hemoglobin <11.0 g/dL, platelets <100,000/μL or absolute neutrophil count (ANC) ≤2,000/μL due to disease, the grading scale proposed by the NCI Working Group on CLL,[24,25] was used; in this scale grade III/IV toxicity is defined as a >50% decrease from baseline.

Statistics

Log-rank tests and proportional hazards regression analysis were used to assess the impact of categorical and numerical factors on median survival, respectively. Kaplan-Meier curves were generated to characterize overall survival and time to disease progression. All statistical computations were carried out using SAS software.

Results

Patients' demographics

Thirty-one patients, aged 43 to 76 years, were entered in the study (Table 1). There were 15 males and 16 females. Of these, 29 patients continued on to full treatment and follow-up; 2 patients were not evaluable for response due to persistent neutropenia following the initial cycle of fludarabine treatment which preceded any IFN therapy. Most (21/31 overall; 21/29 evaluable) patients had stage IV NHL. Fourteen patients had had no prior treatment, while 17 (15 evaluable and the 2 inevaluable) patients had had prior treatment with 1 to 3 different chemotherapy regimens and a median of 1 prior treatment regimen. Eight of 17 (7 of 15 evaluable) patients had been previously treated with anthracycline-containing regimens.

Patients' outcome

The median number of cycles completed for all 31 patients was 4 (range 0 to 8). The median duration of treatment delays was 1 week (range 0 to 7 weeks). Twelve patients completed at least 6 cycles of treatment. The average weekly dose of fludarabine received was 20 mg/m^2, or 96.0% of the expected delivered dose. The average weekly dose of interferon received was 2×10^6 U/m^2, or 89.3% of the expected delivered dose. Of the 29 patients evaluable for response throughout the

Table 1. Patients' demographics (n = 31).

Age (years)	*Number of patients*
Mean	62
Median	61
Range	43-76
Sex	
Male	15
Female	16
Performance status	
0	20
1	9
2	2

Histology Working Formulation	*Corresponding WHO Classification*	*No. of patients*
Small lymphocytic (A)	B-cell SLL/CLL	1
Follicular small cleaved (B)	Follicular NHL grade	16
Follicular mixed small cleaved (C)	Follicular NHL grade 2	11
Diffuse small cleaved (E)	N/A	1
Mantle cell	Mantle cell	2

Stage (Ann Arbor)	Number of patients
II	4
III	6
IV	21
Prior treatment (Median = 1)	Number of patients
0	14
1	9
2	7
3	1

total treatment duration, 15 patients achieved CR/PR (9 treatment-naïve, 6 with a history of prior treatment), with an overall response rate of 51.7% (15/29). The overall response rate including all 31 patients who were initially entered into the study was 48.3% (15/31). Seven had stable disease (3 treatment-naïve, 4 with prior treatment), while 7 had progressive disease (3 treatment-naïve, 4 with prior treatment) (grouped in Table 2). Divided according to histology, there were 5 CR + 5 PR in the 16 patients with IWF B (or follicular lymphoma grade 1 as translated to the WHO classification equivalent) and 1 CR + 3 PR in the 11 patients with IWF C (or follicular lymphoma grade 2). There was one CR in a patient whose pathology was follicular and diffuse small cleaved lymphoma (IWF E) and whose marrow revealed a diffuse infiltration of small cleaved lymphoma cells that was not further characterized by flow cytometry. The median follow-up was 35.6 months, and 13 patients were alive at analysis.

Duration of response, time to progression, and overall survival

We asked whether prior treatment had an impact on response duration, time to progression, and/or overall survival. For the 15 patients who achieved CR/PR (responders), the median response duration was 27.6 months. Treatment-naïve responding patients (n=9) had a median response duration of 39.6 months, whereas the median response duration was 5.2 months for the 6 responding patients who had had prior treatment (p=0.0065). The median time to progression (TTP) for treatment-naive patients was 42.1 months and was 14.5 months for patients who had had prior treatment (p=0.0374). Kaplan-Meier estimates for time to disease progression for all patients are shown in Figure 2, panels A and B. The time to disease progression was significantly shorter in patients who had had prior treatment (p=0.0131); however, overall survival was not significantly affected (p=0.2345). For patients with SD+PD, grouped as non-responders, the median time to progression was 4.1 months, with the median TTP being 5.3 months in the 5 treatment-naïve patients and 3.5 months in the 9 patients who had received prior treatment. Kaplan-Meier estimates are again shown for both TTP and OS (Figure 2, panels C and D), comparing responders (CR+PR) with non-responders (SD+PD), whether previously treated or not. TTP and OS were significantly different between responders and non-responders (p=0.0022 and 0.0167, respectively). Additionally, overall survival for all patients was significantly affected by performance status (PS), being shorter for all patients with PS 1 than for those with a PS of 0 (p=0.0008); however, time to disease progression was not significantly affected by PS (p=0.1189) (*data not shown*). As a single parameter, elevated LDH had a significant impact on both time to disease progression (p=0.0024) and overall survival (p=0.0098). Time to disease progression was, however, found to be significantly longer in those with an International Prognostic Index score of 0 compared with those with an IPI score of 1 and higher (p=0.0378, data not shown). Similarly, patients with elevation of either one or both of LDH and β-2-microglobulin (β2M) had a significantly shorter time to disease progression than those with normal LDH and β2M (p=0.0416, *data not shown*). Overall survival was not affected by IPI or by LDH + β2M (p=0.4680 for IPI, p=0.1095 for LDH + β2M). In addition, in regards to histology, there were no significant differences in response rate, TTP or OS between patients with follicular lymphoma grades 1 versus 2 (p=0.4216 for response rate, p=0.1920 for TTP, and p=0.4469 for OS) (*data not shown*).

Table 2. Median response duration and median time to disease progression for in responders (CR/PR) and non-responders (SD/PD). *p* values of the comparison of response duration, overall survival and time to disease progression between treatment naïve and prior treatment groups for each best response category.

Best Response	*Subset*	*N*	*Response duration (months)*	*comparison p value*	*Time to disease progression (months)*	*comparison p value*	*Overall survival comparison p value*
CR/PR	All patients	N=15	27.6		30.4		
	Treatment naïve	N=9	39.6	0.0065	42.1	0.04	0.56
	Prior treatment	N=6	5.2		14.5		
SD/PD	All patients	N=14	N/A	N/A	4.1		
	Treatment naïve	N=5	N/A	N/A	5.3	0.51	0.88
	Prior treatment	N=9	N/A	N/A	3.5		

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Toxicity

Toxicities for all 31 patients (Table 3) were chiefly myelosuppression, with grade 3 lymphopenia and neutropenia occurring in 14 and 12 patients, respectively, grade 4 lymphopenia in one patient, but no grade 4 neutropenia. Grade 4 thrombocytopenia occurred in one patient, but there were no instances of grade 3 thrombocytopenia. Fever occurred in 19 patients, and grade 1 to 2 infections in six patients. Two patients had to be admitted to hospital because of congestive heart failure, and one each because of neutropenic fever, hypercalcemia, nausea and vomiting, and a new pleural effusion. Time to disease progression and overall survival were significantly affected in patients with grade 2, 3 and 4 anemia, the median TTP being 5.3 months in these patients versus 17.6 months for patients with grade 0 and 1 anemia, and the median overall survival being 15.7 months for the patients with grade 2, 3, and 4 anemia while median OS was not reached during the follow-up period for patients with grade 0 and 1 anemia ($p = 0.0211$ and 0.0130, respectively).

Table 3. Toxicities/side effects: (expressed as numbers of patients with the highest toxicity grade experienced,% of 31 patients in parentheses).

	Grade I	*Grade II*	*Grade III*	*Grade IV*
Lymphopenia	2 (6.4)	13 (41.9)	13 (41.9)	1(3.2)
Neutropenia	6 (1.9)	7 (22.6)	13 (41.9)	0
Anemia	14 (45.2)	10 (32.2)	4 (12.9)	1(3.2)
Thrombocytopenia	7 (22.6)	4 (12.9)	0	1 (3.2)
Fatigue	11 (35.5)	6(19.3)	5 (16.1)	0
Fever	8 (25.8)	8 (25.8)	0	0
Infection	2 (6.4)	3 (9.7)	1 (3.2)	0
Rigors	4 (12.9)	2 (6.4)	0	0
GI				
Stomatitis	0	0	1(3.2)	0
Nausea	9 (29.0)	5 (16.1)	0	0
Diarrhea	1 (3.2)	1 (3.2)	0	0
Anorexia	1 (3.2)	2 (6.4)	0	0
Cardiovascular				
Hypotension	0	0	1 (3.2)	0
Palpitations	10 (32.2)	3 (9.7)	2 (6.4)	0
Neurologic	4 (12.9)	4 (12.9)	1 (3.2)	0
Rash	2 (6.4)	2 (6.4)	0	0
Abnormal liver function tests	1 (3.2)	3 (9.7)	0	0
Weight loss	1 (3.2)	0	0	0
Peripheral edema	0	2 (6.4)	0	0

Discussion

Standard chemotherapy is not curative in LG-NHL. Response rates to fludarabine alone have been reported to be from 28%[5] to 52%[4,6-9] in previously treated patients, with higher response rates reported in previously untreated patients.[10,13] For patients treated with fludarabine as initial chemotherapy, the response lasts between 16 to 24 months.[10-13,26] Despite many studies of IFN, the role of this biological response modifier in the treatment of NHL remains a subject of debate.[27] Many studies have been undertaken incorporating IFN into first line therapy of low-grade NHL, concomitant with initial induction chemotherapy,[27] and for maintenance after chemo-

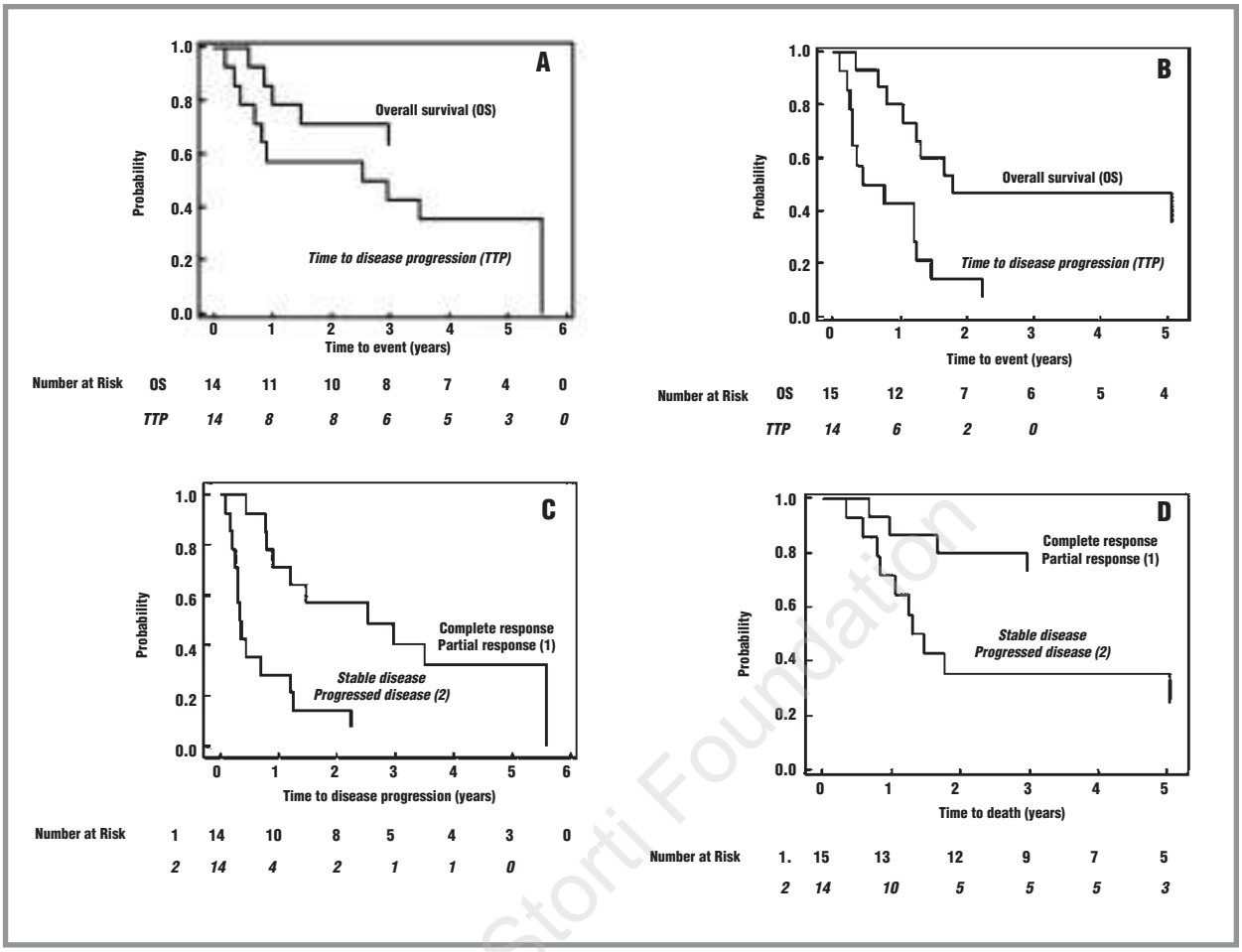

Figure 2. (A,B) Kaplan-Meier estimates for time to disease progression (TTP) and overall survival (OS) for (A) the treatment-naïve group and (B) the group which had had prior treatment. (C,D) Kaplan-Meier estimates for (C) TTP and (D) OS, for responders (complete remissions CR + partial remissions PR) as compared with non-responders (stable disease SD + progressive disease PD). The numbers of patients at risk for each event are given below the plots.

therapy. A recent literature review of trials using IFN with anthracycline-based regimens in combination or as maintenance concluded that both strategies were beneficial.[28] For example, the addition of IFN to a 4-drug doxorubicin-based regimen (COPA) significantly prolonged time to treatment failure.[29] Continued updates of this trial, which included patients with clinically aggressive low-grade as well as intermediate-grade NHL, showed clinically significant improvement in overall survival since the median OS for patients who achieved a CR after chemotherapy alone was 5.7 years whereas it was 7.8 years for those who achieved a CR after chemotherapy and interferon.[30, 31] The benefit of IFN as maintenance treatment is less clear. While a recent SWOG study of 268 patients with LG-NHL showed that the addition of IFN therapy as consolidation therapy for two years after chemotherapy with Pro-MACE-MOPP +/- radiation did not prolong times of progression-free or overall survival,[32,33] Aviles *et al.* reported in 1996 that at a 9-year follow-up, 62% of patients with LG-NHL who had received IFN for one year as maintenance treatment after conventional chemotherapy remained in CR versus 25% in the control group of patients who had received no further IFN after chemotherapy.[34] However, Arranz *et al.*[35] conducted a multicenter controlled trial with double randomization of 155 patients with LG-NHL, 78 of whom received CVP with IFN three times weekly for 3 months and 77 who received CVP alone; responders were re-randomized to receive IFN as maintenance for one year or observation. The addition of IFN to induction CVP produced a longer duration of response and progression-free survival, but there were no differences in OS over a follow-up of 3 years. Furthermore, the duration of response between those receiving IFN as maintenance therapy was similar to that in the control group irrespective of previous treatment.[35] Similar modest benefits from IFN have been found in other studies.[36,37] Hagenbeek *et al.* reported that one year of IFN mainte-

nance therapy after CVP prolonged the time to progression in LG-NHL to a median of 132 weeks versus 87 weeks in those not maintained on IFN therapy; although overall survival was not affected.[36] Mauro *et al*., however, found that of 133 patients with CLL randomized to receive fludarabine/ prednisone alone or followed by IFN therapy, 41 patients who had an initial CR and then received IFN had a longer response than the 37 patients who were simply observed after CR.[38] A recent phase II study of 21 evaluable patients with low-grade NHL showed that patients with a PR after fludarabine/ IFN who then received maintenance IFN had a similar response rate to that of chemotherapy-naïve patients and previously pretreated ones, and have a median response duration of 12 months.[39] The clear benefit of adding IFN to induction chemotherapy or as maintenance remains controversial. Two recent meta-analyses have reported that the addition of IFN to front-line combination chemotherapy, as well as extended as maintenance therapy after induction, both prolongs duration of response and improves overall survival, with the effect being most pronounced in patients whose initial chemotherapy regimens contained anthracyclines or mitoxantrone.[40,41] In keeping with these conclusions, Rohatiner *et al*. also presented in abstract form a meta-analysis of 10 randomized studies of 2005 newly diagnosed NHL patients, and reached similar conclusions on the addition of IFN to an initial doxorubicin- or mitoxantrone-containing chemotherapy regimen, if the IFN dose exceeded 36×10^6 units per 28 days.[42] However, the trials evaluated in these analyses did not necessarily include patients who had received previous treatment, and the optimal duration of IFN therapy has not yet been determined.

In our study, we investigated the effect of fludarabine in an alternating initial schedule with IFN to permit full doses of each agent to be investigated early in the treatment plan for patients with several incurable mature B-cell neoplasms. There was a marked prolongation of response duration, but not overall survival, seen in those patients who were treatment-naïve, compared with those who had had prior treatment. Eight of the 17 previously treated patients had received anthracycline-based therapy. In terms of histology, the time to progression of disease or overall survival was not significantly different in patients with IWF B and IWF C disease (0.0992 and 0.2843, respectively). Although not all slides were re-reviewed at Fox Chase Cancer Center when the WHO classification came into use, these disease states would correspond to WHO follicular lymphoma grades 1 and 2. The two patients with mantle cell lymphoma enrolled in the study did not respond to this therapy, although one did not recover adequate blood counts after the first cycle of fludarabine, never received IFN, and was deemed inevaluable for response. Both had received at least 2 prior treatments and had progressive disease on treatment. There were too few patients in other categories for adequate comparisons. Regarding clinical parameters, only LDH and performance status were prognostic for survival. Time to disease progression was predicted by prior treatment, LDH and IPI score. Otherwise the disease stage and site, the patients' age, gender, and baseline β2-microglobulin, and the average weekly dose of fludarabine or IFN received, had no significant effect on the TTP or OS.

We conclude that this dose and alternating schedule of fludarabine and interferon without maintenance produces a similar response rate to that reported for fludarabine alone.[3-13,26] Although overall survival may not be further improved, the prolonged duration of response in previously untreated patients is intriguing. Given that the toxicities of IFN do not overlap with those of chemotherapy and antibody-based therapeutics, there may be a role for combination therapies in prolongation of remission, especially if the biological basis of response to IFN can be elucidated. A preliminary study has shown that IFN plus the chimeric anti-CD20 monoclonal antibody rituximab in patients with relapsed LG-NHL is relatively well tolerated.[43] Recent reviews raise the questions of whether addition of IFN to rituximab treatment in relapsed or untreated LG-NHL may improve response,[44,45] and whether it may do so by enhancing antibody-dependent cell-mediated cytotoxicity. The treatment of low-grade and mantle cell lymphoma is still challenging, and curative strategies remain to be identified. It will be important to evaluate those immunomodulatory or apoptosis-modulatory combinations which will prolong response in relapsed LG-NHL.

MRS: conceived and designed the protocol, and entered patients in the study; he was fully involved in the analysis and interpretation of the data, and in writing and revising the manuscript; GJM: analyzing the data and writing the manuscript; MMM, RJS: protocol design, patient accrual and manuscript revisions; KPS, GY, TH: data collection, monitoring and analysis; HW, AR: data analysis and AR: statistical design. JC, RLB: entered patients in the study and critiqued the manuscript.

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