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α-INTERFERON AS MAINTENANCE DRUG AFTER INITIAL FLUDARABINE THERAPY FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND LOW-GRADE NON-HODGKIN'S LYMPHOMA

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ABSTRACT

Background. **Fludarabine monophosphate (FLU) is an adenine nucleoside analogue with promising therapeutic activity in lymphoproliferative disorders. In addition, the effectiveness of α-interferon (α-IFN) in low-grade non-Hodgkin's lymphoma (LG-NHL) and B-cell chronic lymphocytic leukemia (B-CLL) has been demonstrated in several clinical trials.**

Methods. **In a phase II study of 45 patients with B-CLL and 28 with LG-NHL, we used FLU as second and third-line chemotherapy. Dosages of 25 mg/m^2 were given in 30-minute infusions for 5 consecutive days. Treatment was repeated every 28 days depending on patients' clinical status for a maximum of 6 cycles. Entrance in the human lymphoblastoid α-IFN maintenance portion of the study depended on response to initial FLU. Following randomization we administered α-IFN, or no therapy at all, to patients who obtained a complete or a partial response after FLU therapy. The α-IFN dose was 3×10^6 U three times per week until disease progression.**

Results. **Twenty-one B-CLL patients achieved major responses, as did 17 of those with LG-NHL. Twenty-four of the former group and 11 of the latter failed to respond or obtained only a minor response. The 38 patients who responded well and entered the second part of the trial showed significant prolongation of remission duration with maintenance α-IFN.**

Conclusions. **In consideration of its significant activity, the role of FLU in the management of lymphoproliferative disorders needs to be evaluated further; at the same time, this preliminary analysis seems to indicate that maintenance α-IFN may extend remission duration in B-CLL and LG-NHL.**

Key words: B-CLL, LG-NHL, fludarabine, α-IFN, maintenance treatment

Fludarabine monophosphate (FLU) is a fluorinated analogue of adenosine arabinoside[1,2] that recently has been used extensively in previously treated and untreated patients with B-cell chronic lymphocytic leukemia (B-CLL)[3-9] and in those with low-grade non-Hodgkin's lymphoma (LG-NHL).[10-14]

α-Interferon (α-IFN) has proven to be effective in several clinical trials involving patients with chronic lymphoproliferative syndromes.[15-19] Recent results have also demonstrated the efficacy of α-IFN when given at the time of diagnosis, but it is not sufficiently active to be recommended as first-line treatment for patients with B-CLL and LG-NHL.

Experience with α-IFN therapy for other

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hematologic disorders, such as hairy cell leukemia,[20, 21] mycosis fungoides,[22, 23] and chronic myeloid leukemia,[24, 25] suggests that prolonged administration of this agent may confer an advantage. The role of α-IFN in the treatment of B-CLL is still unclear. High doses of α-IFN in patients with B-CLL failed to produce satisfactory response while causing significant toxicity.[26] Subsequently, several trials employing low-dose α-IFN therapy were initiated in the early stages of B-CLL and they produced promising results.[27-29]

Price et al. and Mc Laughlin et al.[30, 31] are conducting trials to evaluate α-IFN efficacy in chronic therapy to reduce residual disease and to intensify the responses obtained from conventional therapy in low-burden diseases.

On the basis of these data, we started a phase II trial with FLU in previously heavily treated patients with B-CLL and LG-NHL. The study included a randomization after completion of the first phase for those who had obtained at least a partial response (PR); they received either no further therapy or maintenance α-IFN. Herein we summarize our experience.

Patients and methods

Patient population

From January, 1991 to September, 1992, 73 previously-treated patients (45 with B-CLL and 28 with LG-NHL) were entered in this phase II study. For the LG-NHL group, criteria for entry included: histologic diagnosis of one of the following lymphoma subtypes: centroblastic/centrocytic follicular, centroblastic/centrocytic follicular and diffuse, immunocytoma lymphoplasmacytoid lymphomas according to the Kiel classification,[32] stage IV as outlined by the Ann Arbor Conference;[33] entry criteria for B-CLL patients included stage > II according to the method described by Rai.[34]

Table 1. Patient characteristics.

Total n.	73
Sex M/F	48/25
Median age (range)	58 (40-75)
B-CLL/LG-NHL	45/28
Stage B-CLL:	
Rai stage III	13/45
Rai stage IV	32/45
Stage LG-NHL:	
IV	28/28

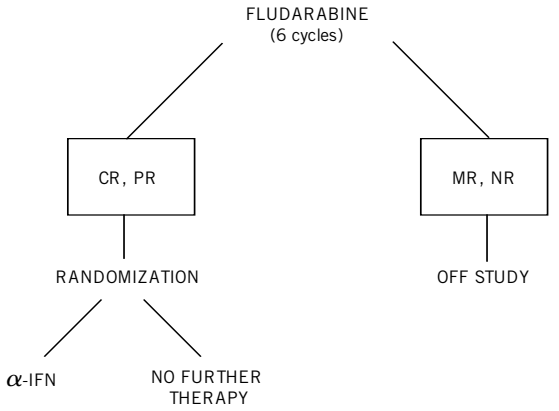

Figure 1. Treatment algorithm of induction and maintenance phases.

Characteristics of patients participating in this study are shown in Table 1.

Fifty patients had received 1-3 treatments, and the remaining 23 more than 3 chemotherapeutic regimens. The time from previous treatment to the start of FLU ranged from 1 to 96 months (median 34 months).

Treatment

The study algorithm is shown in Figure 1.

FLU, supplied by Inveresk Clinical Research Limited (Edinburgh, Scotland), was given at a dose of 25 mg/m^2 per day by 30-minute infusion for 5 consecutive days. Treatment was repeated every 28 days as dictated by peripheral blood counts and clinical status for a maximum of 6 cycles.

Patients were also treated with human lymphoblastoid α-IFN (Wellferon), kindly provided by Wellcome Foundation Limited (Langley Court-Beckenham, Kent BR3 3BS, UK), and all of them received 3×10^6 Units (3 MU) three times per week, self-administered intramuscularly until the disease progressed.

Entry in the maintenance phase of the study was correlated to treatment responses, i.e. only those patients who achieved complete (CR) or partial response (PR) with FLU were admitted. Randomization to maintenance therapy or no maintenance was carried out at a 1:1 ratio. Maintenance therapy with α-IFN was continued until the disease progressed.

Response criteria

B-CLL

A CR was recorded if the peripheral lymphocyte count was less than 4.0×10^9/L and bone marrow examination revealed less than 30% lymphocytes, regression of lymph nodes, hepatosplenomegaly (when present), and recovery of peripheral blood counts (neutrophils > 1.5×10^9/L; platelets > 100×10^9/L; hemoglobin > 11.0 g/dL without transfusion, and a lymphocyte count of < 4.0×10^9/L).

We considered the response to be partial if the circulating lymphocytes were reduced by more than 50% and platelet count was more than 100×10^9/L, or if there was a 50% improvement over baseline (without tranfusions) in the degree of bone marrow infiltration, lymphadenopathy and hepatosplenomegaly. A patient was rated as having a minor response (MR) if a decrease of less than 50% occurred in circulating lymphocytes and in those at all sites of measurable disease. Patients with stable or progressive disease were considered as non-responders (NR).

LG-NHL

A CR was defined as the complete disappearance of signs and symptoms due to disease, as well as normalization of all previously abnormal clinical symptoms.

A reduction of at least 50% of known disease with disappearance of systemic manifestations was rated as a PR. Less than 50% decrease in the size of measurable lesions was designated an MR. Patients with stable and progressive disease were considered as having no response and received no further therapy.

Survival and progression-free survival curves were calculated according to the method of Kaplan and Meier.[35]

Standard Eastern Cooperative Oncology Group toxicity criteria were used.[36]

Table 2. Response according to initial FLU treatment of 45 B-CLL and 28 LG-NHL patients.

	B-CLL	*LG-NHL*	*TOTAL*
CR	1	3	4
PR	20	14	34
MR	10	5	15
NR	14	6	20

Results

Responses to initial treatment

Table 2 depicts the responses to initial FLU treatment. Major responses (CR+PR) were seen in 21 B-CLL and 17 LG-NHL cases (52%). In particular, of the 45 B-CLL patients who were evaluated, 1 achieved a CR, 20 PR, 10 MR, and the remaining 14 did not respond to therapy. Of the 28 patients with LG-NHL, 3 met the criteria for CR and 14 for PR; 5 had MR, and 6 failed to respond. Responses to FLU were rapid and became evident after 2 cycles of treatment.

Responses to maintenance α-IFN

Thirty-eight patients were eligible for entry into the second part of the trial, with 20 entering the α-IFN maintenance arm and 18 receiving no therapy. A breakdown by disease showed that 21 had B-CLL and 17 had LG-NHL.

Remission duration according to maintenance therapy is shown in Figure 2 for those patients who achieved major responses to initial therapy. The median follow-up was 16 months (range 3 to 19) and the P value was 0.2.

Among patients randomized to α-IFN maintenance, 6 of 20 (30%) progressed while receiving the drug, whereas 10 of 18 (55%) of those receiving no therapy showed disease progression during the maintenance period. However, none of the patients in CR relapsed (they were equally distributed: 2 for each arm). No relationship between progression rate and disease (B-CLL or LG-NHL) was observed. In fact, we found 9 of 21 (43%) progressed in the B-CLL group and 7 of 17 (41%) among those with LG-NHL.

Toxicity

Fludarabine. Neutropenia, the main hematologic toxic effect, was observed in 42 of the 73 patients; 22, 15, 2 and 3 had grade 1, 2, 3, 4, respectively. No case of severe thrombocytopenia related to FLU was recorded. Other major side effects noted were infections and febrile episodes. Fever of undetermined origin occurred in 15. Of the 14 patients who experi-

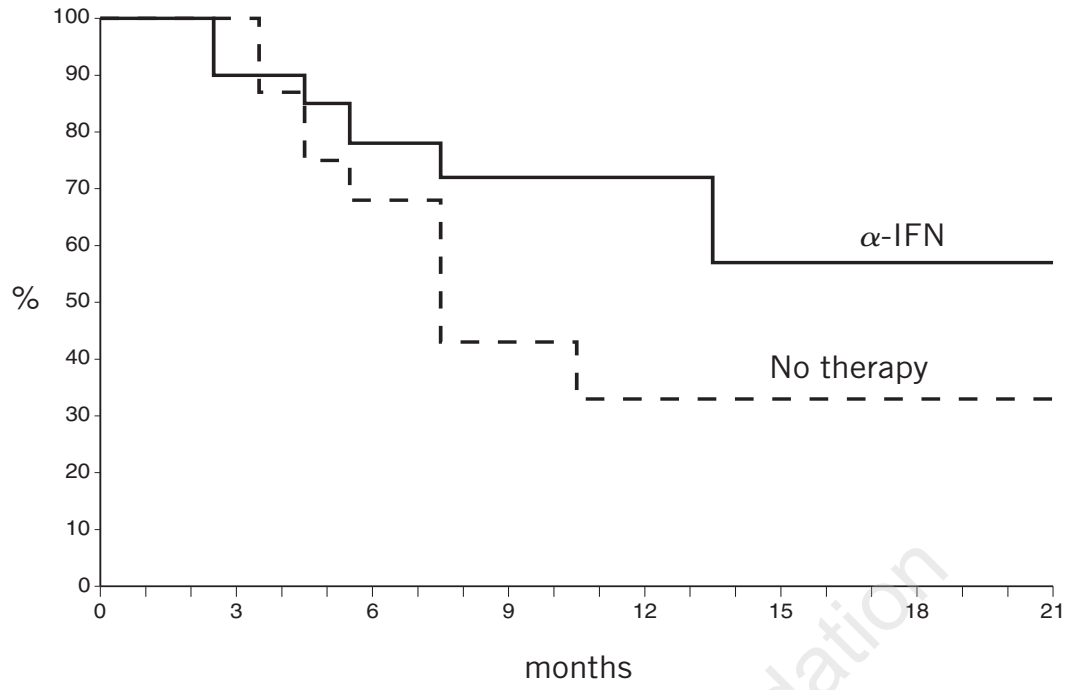

Figure 2. Remission duration during the randomized maintenance phase for the 38 patients who obtained major responses (CR+PR) with FLU induction therapy.

enced infections, 6 required symptomatic treatment or oral antibiotics, 4 required parenteral antibiotics and/or hospitalization, and 4 died. All major infections involved the respiratory tract or sinuses. The 4 deaths were attributed to staphylococcal septicemia (2 patients) and respiratory tract infections that were probably of bacterial origin (2 patients).

Additional side effects were mild and consisted of nausea-vomiting (1 patient), renal and liver toxicities (grade 1 in two patients), and a local skin reaction in 5 patients.

α-IFN. Fifteen patients initially experienced subjective systemic symptoms from α-IFN: fever (10 cases), myalgia and arthralgia (4 cases), nausea, vomiting and weight loss (1 case); only 1 patient had to discontinue taking the drug because of nausea and vomiting.

Discussion

Our findings demonstrate that FLU as a single agent exerts an evident therapeutic effect in patients with relapsed and/or refractory B-CLL and LG-NHL, producing an overall response rate of 52%. Differential overall response rates were 47% and 60% for B-CLL and LG-NHL patients, respectively.

Despite their indolent outcome and/or positive response to alkylating agents, LG-NHL and B-CLL often become resistant to these drugs or progress more aggressively. New drugs are needed for this aggressive phase, and the relatively recent advent of purine analogues represents an effective alternative to alkylating agents and prednisolone. In particular, FLU has been shown to produce sustained remission in B-CLL,[3-9] in LG-NHL,[9-14] and in other lymphoproliferative disorders.[37-39] The side effects of this regimen were acceptable, with febrile episodes and infections occurring most frequently. Some of the patients had varying degrees of neutropenia at the start of therapy that made it difficult to assess the contribution of FLU to the infectious episodes.

In the second part of this study, we tested the role of α-IFN as maintenance therapy in these diseases. We kept in mind that these patients were all relapsed and/or refractory to conventional treatments. As previously described, the benefits of α-IFN in B-CLL and LG-NHL[30, 31, 40] have been most apparent in the context of protracted therapy and low-volume disease.

A prolongation of remission was seen with maintenance α-IFN: only 6 of 20 patients

(30%) in this arm relapsed versus 10 of 18 (55%) of those with no maintenance.

Although the results of our study are preliminary and the small number of patients and limited follow-up prevent definite conclusions, one observation is already apparent: it seems that α-IFN may play a role as maintenance treatment in low-burden disease patients with B-CLL and LG-NHL. In addition, the benefits of this strategy justify the inconvenience of three weekly α-IFN injections.

If the present findings are confirmed by further patient accrual and longer follow-up, they will provide a starting point for additional research.

On the basis of these data and those reported by other investigators,[3-14] FLU as a single agent is associated with a significant response rate in relapsed and advanced B-CLL and LG-NHL patients. So far, it is clear that FLU induces remission in at least 50% of such previously treated cases. It will now be important to test FLU in combination with standard polychemotherapy or with other purine analogues or with cytokines in pretreated and untreated patients.

At the same time, this preliminary analysis seems to suggest that maintenance α-IFN prolongs remissions after treatment with FLU. Furthermore, α-IFN toxicity is generally tolerable and does not overlap with the toxic effects of conventional cytotoxic agents. We believe that our findings confirm the pivotal role of α-IFN in the management of lymphoproliferative diseases. They also encourage the use of α-IFN as long-term therapy in the management of chronic lymphoproliferative disorders and its use in conjunction with other primary and secondary therapy drugs. In the coming years, further clinical trials will serve to strengthen the role of α-IFN as maintenance treatment in the management of chronic lymphoproliferative disorders.

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