Fludarabine-based chemotherapy in untreated mantle cell lymphomas: an encouraging experience in 29 patients

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Abstract

Background and Objectives. A prospective study to evaluate the role of fludarabine alone or in combination with idarubicin in untreated patients with mantle cell lymphoma (MCL).

Design and Methods. Twenty-nine untreated patients with mantle cell lymphoma were stochastically treated with intravenous fludarabine at a dose of 25 mg/m²/day for 5 days (11 patients) or with a combination of fludarabine and idarubicin (FLU-ID) (fludarabine 25 mg/m² i.v. on days 1 to 3 and idarubicin 12 mg/m² i.v. on day 1 (18 patients). For both regimens, cycles were given at three-week intervals for a total of six courses. According to the International Prognostic Index, the most part of high-intermediate and high risk factor patients were in the FLU-ID subset: 7 (39%) patients vs. 2 (18%) in the fludarabine alone subset.

Results. Of the 29 patients, 8 (28%) obtained a complete response and 10 (35%) a partial response, with an overall response rate of 63%. The remaining 11 (37%) patients did not respond to the therapy. The overall response rates were 64% (7 patients) in the fludarabine group and 61% (11 patients) in the FLU-ID group. The complete response rate was 27% (3 patients) for fludarabine and 28% (5 patients) for FLU-ID. The toxicity was mild in terms of neutropenia and infections, and no fatalities occurred due to drug-induced side effects.

Interpretation and Conclusions. These results suggest the efficacy of fludarabine alone or in combination with idarubicin in MCL patients. It will be important to increase this experience and to assess other fludarabine-containing regimens, in particular with cyclophosphamide plus idarubicin and with mitoxantrone and or cyclophosphamide, to test the true role of this approach in MCL.

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Key words: mantle cell lymphoma, fludarabine, fludarabine in combination, idarubicin, complete response

Two clinical trials are currently being performed in order to help to define the therapeutic efficacy and toxicity of these two regimens in patients with untreated MCL.
Design and Methods

Between December 1995 and July 1998, 29 previously untreated MCL patients entered this prospective study. The criteria for entry included: diagnosis of MCL based on a combination of morphologic and immunologic criteria, according to the European Lymphoma Task Force; central histologic diagnosis reassessment through immunohistochemical analysis before study entry; stage II-IV disease as outlined by the Ann Arbor Conference; the presence of measurable disease; normal hepatic, renal, and cardiac function; HIV negativity. Informed consent was obtained from all patients in accordance with the ethical policies of the institutes involved.

Staging was evaluated by bone marrow biopsy (including immunohistochemical analysis), immunophenotypic profile of the peripheral blood, and hematologic and chemical survey, in addition to chest radiograms, abdominal ultrasonography and computerized tomography of the chest and abdomen in all patients. Lactate dehydrogenase (LDH) was always determined.

The study design included a solely stochastic determination at diagnosis of which treatment the patient would receive, either fludarabine alone or fludarabine plus idarubicin (FLU-ID regimen). No randomization list was used. The fludarabine-alone schedule was 25 mg/m\(^2\)/day intravenously (IV) over 30 minutes for 5 consecutive days. The FLU-ID regimen schedule was as follows: fludarabine 25 mg/m\(^2\)/day IV on days 1 to 3, and idarubicin 12 mg/m\(^2\)/day IV on day 1. For both regimens, cycles were given at three-week intervals for a total of 6 courses. Fludarabine was supplied by Schering S.p.A. (Milan, Italy). All patients received Pneumocystis carinii prophylaxis with cotrimoxazole (2 consecutive days per week) during the entire course of treatment. All patients were restaged after completion of 6 cycles; clinical and pathologic evaluations were made by repeating radiographic investigations and bone marrow biopsy.

Patients' characteristics

The median age was 57 yrs (range 30 to 71 yrs). Of the 29 patients, 18 were males and 11 females. A considerable percentage of patients had clinically aggressive disease: in particular 24/29 (83%) had stage III or IV disease, 21/29 (73%) had bone marrow involvement, 13/29 (45%) had one or more extranodal sites involved, and 4/29 (14%) had bulky disease. LDH was elevated in 5 (17%) patients; good performance status (0/1) was present in all cases. Histologic examination showed a diffuse architectural pattern in all cases. Morphologically, cells were small to medium in size in 20 (69%) cases, small and round in 7 (24%) patients, and large and blastic in the remaining 2 (7%) cases. According to the International Prognostic Index, 2 (7%) patients had no adverse factors, 9 (31%) had one factor, 9 (31%) had two factors, six (21%) had three adverse parameters, and 3 (10%) had four factors; no patient had all five negative parameters.

Response criteria

Complete response (CR) was defined as a complete disappearance of signs and lymphoma-associated symptoms that was maintained for at least six weeks. A reduction by at least 50% of known disease with disappearance of systemic manifestations for a duration of at least six weeks was defined as partial response (PR). Patients with progressive disease during chemotherapy administration or within 6 weeks from its completion were considered as having no response and received no further therapy.

The survival curve was measured from entry into the protocol until death; the relapse-free interval was calculated from the date of response until relapse or death. Survival and relapse-free survival curves were calculated according to the method of Kaplan and Meier. Standard Eastern Cooperative Oncology Group toxicity criteria were used.

Results

The International Prognostic Index of the patients in the two treatment groups was not similar. Most of the patients treated with fludarabine alone were classified as low or low-intermediate risk (9/11, 82%) while in the FLU-ID subset 7/18 (39%) patients had a high-intermediate or high risk (Table 1).

Response to treatment

Treatment outcome is summarized in Table 2. Of the 29 patients studied, 8 (28%) fulfilled the criteria for CR and 10 (35%) for PR, with an overall response rate of 63%. The remaining 11 (37%) patients did not respond.
respond to therapy. In the fludarabine group, the overall response rate (CR plus PR) was 64% (7 patients), that in the FLU-ID group was 61% (11 patients). The CR rate as defined above was 27% (3 patients) in those treated with fludarabine and 28% (5 patients) in those with FLU-ID.

Of the 8 patients who achieved CR, 2 (25%) relapsed: a fludarabine patient after 14 months and a FLU-ID patient after 7 months. The remaining 6 patients are still in remission after 4 to 24 months (median, 13 months).

The overall survival (Figure 1) at 24 months was 57%(median 20 months; range 6-32 months). Figure 2 shows the probability of relapse-free survival at 24 months (median 15 months; range 3-23 months), which turned out to be 56%.

With respect to histology, both patients with the blastoid variant of the disease (one in each treatment group) were non-responders. Of the 3 high risk patients, as evaluated by International Prognostic Index criteria, only 1 (33%) achieved a CR. In the 6 high-intermediate risk patients, 1 (17%) CR was documented, while among the 9 patients with low-intermediate risk, 3 CRs (33%) were recorded. In the low risk subset 3/11 patients (27%) obtained a CR and six achieved a PR giving an overall response rate of 82%. The response rates according to the different prognostic factors subsets, as defined by the International prognostic Index, are shown in Table 2.

Toxic effects
Granulocytopenia of ECOG scale ≥ 3 was observed in 18/152 (11.8%) courses; thrombocytopenia of ECOG scale ≥ 3 was observed in 1/152 (0.7%) courses. No trend toward cumulative myelosuppression was recorded. No differences between the two therapeutic groups was observed. No patient had infection of ECOG scale ≥ 3. Two episodes of pneumonia were recorded. Nausea/vomiting was rare and mild. No patient developed alopecia. Cardiac, liver, and renal side effects were not observed, and no fatalities attributable to drug toxic effects occurred.

Discussion
Fludarabine given alone has been demonstrated to be an effective therapy for treated and untreated patients with indolent non-Hodgkin's lymphomas and gives relatively high response rates, including CRs. Combination therapy with other agents has also been assessed in previously treated patients and, more recently, as initial treatment. The early studies of indolent lymphomas included very few patients with MCL. Decaudin et al. reported the first data concerning MCL treated with fludarabine alone, although the majority of these patients had been previously treated. To our knowledge, our study is the first to test fludarabine alone or in combination with idarubicin in untreated MCL patients.

Our data on 29 MCL patients who received fludarabine alone or in combination with idarubicin (FLU-ID) as first therapy showed a global CR rate of 28% with an equivalent therapeutic efficacy for fludarabine alone and FLU-ID; it must be remembered that in the FLU-ID subset 39% of the patients had poor prognostic factors compared to only 18% of the patients treated with fludarabine alone. In terms of overall response, the global rate was 63%, with individual rates of 64% in the fludarabine group and 61% in the FLU-ID group. Tolerance was good and was comparable in the two therapeutic subgroups. Utilizing the specific prophylaxis scheme, no Pneumocystis carinii cases were recorded.

The only previously published data concerning the role of fludarabine in MCL patients were reported by Decaudin et al. All but two of their patients had been pretreated, and all received fludarabine alone. The authors reported a PR rate of 33% but no instances of CR. Our results suggest that if fludarabine is used at diagnosis, CRs can be obtained and the overall response rate can be improved. In fact, with fludarabine used alone in a similar way to that by Decaudin et al., we obtained a 64% overall response rate.
response and a 27% CR rate. These data are similar to those observed in follicular lymphomas, in which fludarabine alone produced responses (mainly PR) in 40-50% of previously treated patients. On the other hand, when fludarabine was investigated as first line treatment it produced a 37% CR rate and an overall response rate of 65%.

The fludarabine/mitoxantrone-based regimen (FN) has been shown to be highly active (overall response rate of 83-94% with a CR rate of 35%-47%) in patients with recurrent or relapsed indolent lymphoma; in addition, utilizing this regimen in untreated follicular lymphoma patients it is possible to obtain a 70-80% rate of CR with bcl-2 negativity in a subset of patients.

On the basis of these data, it will be interesting to use this scheme in untreated MCL patients because the reports regarding pretreated patients included only a few with MCL. In addition, interesting preliminary data on a fludarabine/mitoxantrone/cyclophosphamide-based regimen (FCM), encourage the use of trials of this regimen in MCL patients.

In conclusion, our data on fludarabine alone or in combination with idarubicin indicate that this purine analog is an effective treatment of MCL. This suggests that fludarabine-containing regimens could play an interesting role in MCL. For this reason, it is necessary to increase experience with fludarabine alone or FLU-ID regimens and evaluate the role of other polychemotherapy fludarabine-based regimens, such as FN and FCM, in MCL patients, and the potential combination of fludarabine, idarubicin and cyclophosphamide. If, as seems likely, such studies confirm that fludarabine-based regimens can play a role in first-line treatment of MCL, the response might later be consolidated by immunotherapy (rituximab) or even a flavopiridol-based therapy. The latter, which is still under phase I study, acts by a specific mechanism on the cell cycle.

In any case, we believe that fludarabine-based regimens may emerge to have a real role for a particular subset of MCL patients, and that it would be premature to shelve this therapeutic approach before possible drug combinations have been adequately investigated.

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PLZ was the principal investigator involved in the conception of the study, its design, and the writing of the paper. MM and FG helped the principal investigator (PLZ) with the data analysis interpretation. LM, RB, FR, ADR, AZ, PG, LG, CC, PPF, M Be, M Bo and EA collected the study data. ST critically revised the paper and gave the final approval for its submission.

Disclosures
Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

References