Haematologica 1999; 84:1002-1006 original paper

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

PIER LUIGI ZINZANI, MASSIMO MAGAGNOLI, LUCIANO MORETTI, RAFFAELE BATTISTA, FIORAVANTE RONCONI, AMALIA DE RENZO, ALFONSO ZACCARIA, PATRIZIA GENTILINI, LUCIANO GUARDIGNI, FILIPPO GHERLINZONI, CLAUDIA CELLINI, PIER PAOLO FATTORI, MAURIZIO BENDANDI, MONICA BOCCHIA, ENRICO AITINI, SANTE TURA

Institute of Hematology and Medical Oncology "Seràgnoli", University of Bologna, Bologna; Division of Hematology, Pesaro Hospital, Pesaro; Division of Hematology, Dolo Hospital, Dolo; Division of Hematology, Avellino Hospital, Avellino; Chair of Hematology, University of Napoli, Napoli; Division of Hematology, Ravenna Hospital, Ravenna; Division of Oncology, Forlì Hospital, Forlì; Division of Hematology, Cesena Hospital, Cesena; Division of Oncology, Rimini Hospital, Rimini; Division of Oncology, Mantova Hospital, Mantova, Division of Hematology, Siena Hospital, Siena, Italy

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.**

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

Correspondence: Pier Luigi Zinzani, M.D., Istituto di Ematologia e Oncologia Medica "Seràgnoli", Policlinico S.Orsola, via Massarenti 9, 40138 Bologna, Italy. Phone: international +39.051.390413 – Fax: international +39.051.398973.

Mantle cell lymphoma (MCL) has been recognized by the *International Lymphoma Study Group and the European Lymphoma Task Force* as a distinct histologic and clinical entity on the basis of its morphologic, immunophenotypic, cytogenetic, and molecular genetic characteristics.[1-3] Diagnosis of MCL by means of histology alone is often difficult and phenotypic evidence ($CD20^+$, $CD5^+$, $CD10^-$, $CD23^{-/+}$) is required.[4,5]

Among the malignant lymphomas, MCL is characterized by an unfavorable prognosis with a moderate sensitivity to chemotherapy and a median survival of only 3-4 years. Attempts to improve the dismal outlook for MCL patients, most of whom are elderly, by more intensive and/or anthracycline-containing combinations have resulted in somewhat higher remission rates but have not proven beneficial in terms of overall survival.[6-9] New approaches are therefore amply warranted, and pilot sudies have been initiated to investigate new agents such as epipodophyllotoxins and purine analogs. Among the purine analogs, both *in vitro* and *in vivo* studies with fludarabine have highlighted apoptosis as an important additional mode of fludarabine-induced cell death. In the last few years, fludarabine has been used extensively in indolent lymphomas[10-15] producing overall response rates ranging from 40% to 70% in pretreated and untreated patients. Several groups have recently conducted preliminary trials involving a combination of conventional cytotoxic drugs (mitoxantrone, idarubicin, cyclophosphamide) with fludarabine in order to enhance the antineoplastic activity of the latter:[16-22] an 80-90% response rate was obtained with a higher fraction of complete responders.

Considering that very little information is available on the possible efficacy of fludarabine, alone or in combination, in untreated MCL patients, we studied this efficacy by stochastically allocating our patients to be treated with either fludarabine alone or fludarabine plus idarubicin. Here, we report the results obtained in our first 29 consecutive patients, 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*;[3] central histologic diagnosis reassessment through immunohistochemical analysis before study entry; stage II-IV disease as outlined by the Ann Arbor Conference;[23] 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 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 blastoid in the remaining 2 (7%) cases. According to the International Prognostic Index,[24] 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.[25] Standard Eastern Cooperative Oncology Group toxicity criteria were used.[26]

Results

The International Prognostic Index[24] 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

Table 1. All 29 MCL patients according to the International Prognostic Index.

	Fludarabine (%)	*FLU-ID (%)*	*Overall (%)*
Low risk	6/11 (54)	5/18 (28)	11/29 (38)
Low-intermediate risk	3/11 (28)	6/18 (33)	9/29 (31)
High-intermediate risk	2/11 (18)	4/18 (22)	6/29 (20)
High risk	0	3/18 (17)	3/29 (11)

Table 2. Response rate of the 29 MCL patients.

	Fludarabine		*FLU-ID*		*Overall*	
	CR	*PR*	*CR*	*PR*	*CR*	*PR*
Low risk	2/6	3/6	1/5	3/5	3/11	6/11
Low-intermediate risk	1/3	1/3	2/6	2/6	3/9	3/9
High-intermediate risk	0/2	0/2	1/4	1/4	1/6	1/6
High risk	/	/	1/3	0/3	1/3	0/3
Overall	3/11	4/11	5/18	6/18	8/29	10/29

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[24] 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,[24] 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[10-22] 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.[27,28] The early studies of indolent lymphomas included very few patients with MCL. Decaudin *et al.*[29] 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*.[29] 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

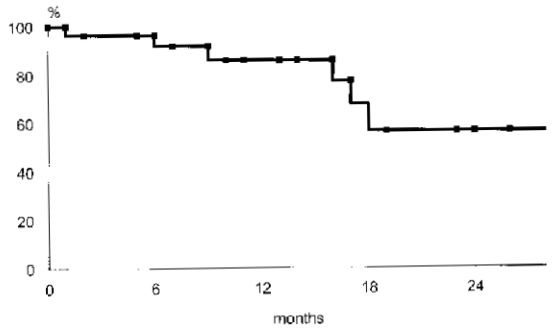

Figure 1. Overall survival curve of all 29 MCL patients.

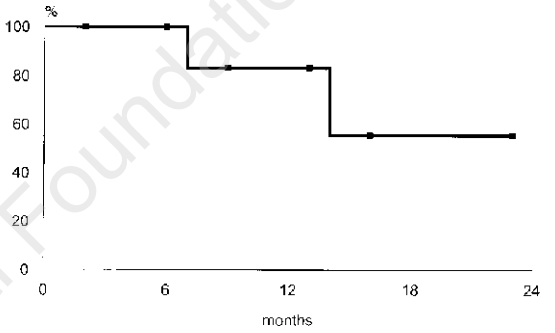

Figure 2. Relapse-free survival curve of the 8 MCL patients who obtained a CR.

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.[10-14] 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%.[15]

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[16-20] 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.[27] On the basis of these data, it will be interesting to use this scheme in untreated MCL patients because the reports regarding pretreated patients[16-20] included only a few with MCL. In addition, interesting preliminary data on a fludarabine/mitoxantrone/cyclophosphamide-based regimen (FCM),[30] 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)[31] or even a flavopiridol-based therapy.[32] 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.

Contributions and Acknowledgments

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, MBe, MBo 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.

Manuscript processing

Manuscript received March 23, 1999; accepted July 20, 1999.

References

1. Banks PM, Chan J, Cleary ML, et al. Mantle cell lymphoma. A proposal for unification of morphologic, immunologic and molecular data. Am J Surg Pathol 1992; 16:637-40.
2. Harris NL, Jaffe ES, Stein H, et al. A revised European-American Classification of lymphoid neoplasms. A proposal from the International Lymphoma Study Group. Blood 1994; 84:1361-92.
3. Zucca E, Stein H, Coiffier B. European Lymphoma Task Force (ELTF): Report of the workshop on Mantle Cell Lymphoma (MCL). Ann Oncol 1994; 5:507-11.
4. Weisenburger DD, Armitage JO. Mantle Cell Lymphoma: an entity comes of age. Blood 1996; 87:4483-94.
5. Lardelli P, Bookman MA, Sundeen J, et al. Lymphocytic lymphoma of intermediate differentiation: morphologic and immunophenotypic spectrum and clinical correlations. Am J Surg Pathol 1990; 14:752-63.
6. Berger F, Felman P, Sonat A, et al. Nonfollicular small B-cell lymphomas: a heterogenous group of patients with distinct clinical features and outcome. Blood 1994; 83:2829-35.
7. Meusers P, Engelhard M, Bartels H, et al. Multicentre randomized therapeutic trial for advanced centrocytic lymphoma: anthracycline does not improve the prognosis. Hematol Oncol 1989; 7:365-80.
8. Bertini M, Rus C, Freilone R, et al. Mantle cell lymphoma: a retrospective study on 27 patients. Clinical features and natural history. Haematologica 1998; 83:312-6.
9. Zucca E, Roggero E, Pinotti G, et al. Pattern of survival in mantle cell lymphomas. Ann Oncol 1995; 6:257-62.
10. Redman JR, Cabanillas F, Velasques WS, et al. Phase II trial of fludarabine phosphate in lymphoma: An effective new agent in low-grade lymphoma. J Clin Oncol 1992; 109:790-4.
11. Hochster HS, Kim K, Green MD, et al. Activity of fludarabine in previously treated non-Hodgkin's lymphoma: Results of an Eastern Cooperative Oncology Group study. J Clin Oncol 1992; 10:28-32.
12. Zinzani PL, Lauria F, Rondelli D, et al. Fludarabine: An active agent in the treatment of previously-treated and untreated low-grade non-Hodgkin's lymphoma. Ann Oncol 1993; 4:575-8.
13. Hiddeman W, Unterhalt M, Pott C, et al. Fludarabine single-agent therapy for relapsed low-grade non-Hodgkin's lymphomas: A phase II study of the German low-grade non-Hodgkin's lymphoma study group. Semin Oncol 1993; 20:28-31.
14. Pigaditou A, Rohatiner AZS, Whelan JS, et al. Fludarabine in low-grade lymphoma. Semin Oncol 1993; 20:24-7.
15. Solal-Cèligny P, Brice P, Brousse N, et al. Phase II trial of fludarabine monophosphate as first-line treatment in patients with advanced follicular lymphoma: a multicenter study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1996; 14:514-9.
16. McLaughlin P, Hagemeister FB, Swan F, et al. Phase I study of the combination of fludarabine, mitoxantrone, and dexamethasone in low-grade lymphoma. J Clin Oncol 1994; 12:575-9.
17. Pott C, Unterhalt M, Sandford D, et al. Fludarabine as

single agent and in combination with mitoxantrone and dexamethasone in relapsed and refractory low-grade non-Hodgkin's lymphoma. Ann Haematol 1994; 68 (Suppl.1):A3.
18. Zinzani PL, Bendandi M, Tura S. FMP regimen (fludarabine, mitoxantrone, prednisone) as therapy in recurrent low-grade non-Hodgkin's lymphoma. Eur J Haematol 1995; 55:262-6.
19. McLaughlin P, Hagemeister FB, Romaguera JE, et al. Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. J Clin Oncol 1996; 14:1262-8.
20. Zinzani PL, Bendandi M, Magagnoli M, et al. Fludarabine mitoxantrone combination-containing regimen in recurrent low-grade non-Hodgkin's lymphoma. Ann Oncol 1997; 8:379-83.
21. Zinzani PL, Bendandi M, Gherlinzoni F, et al. FLU-ID (fludarabine and idarubicin) regimen as salvage therapy in pretreated low-grade non Hodgkin's lymphoma. Haematologica 1996; 81:168-71.
22. Hochster H, Oken M, Bennet J, et al. Efficacy of cyclophosphamide (CYC) and fludarabine (FAMP) as first line therapy of low-grade non Hodgkin's lymphoma (NHL)-ECOG 1491. Blood 1994; 84(Suppl 1):383a.
23. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971; 31:1860-1.
24. Shipp M, Harrington D, Anderson J, et al. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329:987-94.
25. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958; 53: 457-81.
26. Oken M, Creech R, Tormey D. Toxocity and response criteria of the Eastern Cooperative Oncology Group. Am J Clinic Oncol 1982; 5:649-55.
27. Keating MJ, McLaughlin P, Cabanillas F. Low-grade non-Hodgkin's lymphoma - a development of a new effective combination regimen (fludarabine, mitoxantrone and dexamethasone; FND). Eur J Cancer Care 1997; 6:21-6.
28. Zinzani PL. Idarubicin in low-grade non-Hodgkin's lymphomas. Haematologica 1997; 82 (Suppl to n.5): 23-4.
29. Decaudin D, Bosq J, Tertian G, et al. Phase II trial of fludarabine monophosphate in patients with mantle-cell lymphomas. J Clin Oncol 1998; 16:579-83.
30. Montserrat E, Perales M, Cobo F, et al. Fludarabine, cyclophosphamide and mitoxantrone (FCM) in resistant or relapsed chronic lymphocytic leukemia (CLL) or follicular lymphoma (FL). Ann Hematol 1998; 77 (Suppl I):A6.
31. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92:1927-32.
32. Arguello F, Alexander M, Sterry JA, et al. Flavopiridol induces apoptosis of normal lymphoid cells, causes immunosuppression, and has potent antitumor activity in vivo against human leukemia and lymphoma xenografts. Blood 1998; 91:2482-90.