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Response to fludarabine in B-cell chronic lymphocytic leukemia patients previously treated with chlorambucil as up-front therapy and a CHOP-like regimen as second line therapy

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Background and Objectives. Fludarabine (FAMP) is the most active single agent in relapsed and refractory patients with B-cell chronic lymphocytic leukemia (B-CLL). However, it is not clear whether it should be used immediatly after failure of chlorambucil (CLB). We addressed such an issue retrospectively analyzing a series of patients in whom FAMP was used as third-line therapy after a sequential use of CLB and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like regimen, respectively.

Design and Methods. On a retrospective basis, 57 B-CLL patients fulfilling the above mentioned criteria and followed-up in seven different hematologic institutions, were evaluated.

Results. Of 57 patients who were evaluated for response, 3 (5.2%) achieved a complete response (CR), 30 (52.6%) had a partial response (PR) and the remaining 24 (42.1%) failed to respond to FAMP. Overall median survival from the start of FAMP therapy was 30 months. Survival by tumor response did not show any difference between responders and non-responders (p = 0.536). The survival was significantly shorter in the group of patients with progressive disease than in all other patients included in our study (p = 0.05). Using each patient as his own control (McNemar test) we attempted to evaluate the value of FAMP in inducing a therapeutic response after failure of previous therapies. Among the 37 patients resistant to CLB the response rate was 40.3% with FAMP (p = 0.037) and only 17.5% with CHOP (p = 1.0). Among 35 patients resistant to a CHOP-like regimen, the response rate was 29.8% (p = 0.066) after FAMP therapy.

Interpretation and Conclusions. From our results, it seems that FAMP works better than a CHOP-like regimen in patients resistant to CLB although results do not translate into a survival advantage for responders.

Key words: CLL, fludarabine, third line therapy.

B-cell chronic lymphocytic leukemia (B-CLL) is the most common adult leukemia[1] for which therapeutic options are unsatisfying as cure has remained elusive.[2,3] Until recently, initial treatment of patients with symptomatic B-CLL has often involved therapy with chlorambucil (CLB) with or without prednisone.[4,5] A combination of chemotherapy regimens including anthracyclines, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like (including an anthracycline other than doxorubicin) regimens, has improved response rates in advanced CLL, which range from 40 to 86% in published reports, but without a benefit in terms of survival.[6-9] In this scenario the advent of purine analogs brought renewed hope for the treatment of CLL. Introduced intially by

Grever *et al.*,[10] fludarabine (FAMP) has been the most frequently studied purine analog in B-CLL and probably the most efficacious. The results from several large phase II studies led by the MD Anderson Leukemia group[11,12] and others[13] in previously treated B-CLL patients showed response rates of 52-57%. These promising results led to several comparative trials by North American,[14] French and German investigators.[15] However, FAMP as an up-front therapy for symptomatic B-CLL patients has not been accepted. The use of FAMP as salvage therapy for relapsing and/or refractory B-CLL patients right after failure of alkylating agents or later is not clear.[16-19] With this in mind we retrospectively analyzed results of 57 patients who received FAMP in a relapsing or resistant phase of their disease. The peculiarity of our patient cohort lies in the utilization of FAMP after a sequential use of CLB and CHOP or CHOP-like regimens. So, using each patient as his or her own control it was possible to establish the activity of FAMP in relationship to response to previous therapy. In other words we tried to address the issue of when to give FAMP to patients followed up in the setting of clinical practice.

Design and Methods

Patients

Fifty-seven B-CLL patients treated in seven hematologic institutions form the basis of this study. There were 42 males and 15 females and their median age was 59.6 years (range 36-76). The main clinical characteristics of these patients at the start of FAMP therapy are shown in Table 1. In all cases diagnostic criteria fulfilled those of the revised National Cancer Institute (NCI) Working Group for the diagnosis of B-CLL.[20] According to Rai clinical staging[21] the patients' distribution was as follows: stage II, 27 (47.3%); stage III, 10 (17.5%); stage IV, 20 (35%). According to a subdivision into prognostic groups,[20] 27 patients belonged to the intermediate risk group, and 30 to the high risk one. As far as concerns the time elapsing from the diagnosis to the start of FAMP treatment, this ranged between 10 and 139 months (median, 56 months). Thirty-three (57.8%) patients had resistant disease while 24 (42.1%) patients had relapsed after a previously responsive phase.

Treatment regimen

Before the start of FAMP therapy, a therapeutic sequence which included the CLB as up-front therapy and a CHOP or CHOP-like regimen as second-line therapy was used in all the patients. CLB was given on an intermittent basis and the calculated mean cumulative dose was 943 mg/patient (280-3710) (in 13 courses) while the cumulative dose of doxorubicin was 466 mg/patient (200–600) (in 8 courses, range 4–12).

Table 1. FAMP 3rd line treatment: B-CLL patients' characteristics at the start of FAMP therapy.

	No. (%)
No. patients	57
Sex, male/female	42/15
Age, median	59.6
Age, range	36-76
<55	18 (31.5)
>55	39 (68.4)
Rai Stage	
II	27 (47.3)
III	10 (17.5)
IV	20 (35.0)
Prognostic groups	
intermediate risk	27 (47.3)
high risk	30 (52.6)

FAMP: fludarabine; B-CLL: B-chronic lymphocytic leukemia.

FAMP was administered on an outpatient basis at standard doses of 25 mg/m^2/day intravenously for 5 days, every four weeks. The median number of FAMP cycles was 5 (range 4–12). Overall a mean cumulative dose of 875 mg/patient (range 700–2100) was given.

Response criteria

Response criteria were those recommended by the NCI Working Group:[20] complete remission (CR) was defined as the disappearance of palpable masses, the recovery of satisfactory blood parameters (neutrophils > 1.5×10^9/L, platelets >100×10^9/L, hemoglobin > 11 g/dL, lymphocytes < 4×10^9/L), and lymphocyte bone marrow (BM) infiltration lower than 30%. Partial remission (PR) was defined as a > 50% decrease both in palpable masses and peripheral blood lymphocytosis, as well as a > 50% improvement of one or more of the blood parameters. Patients with progressive or stable disease were considered as non-responders at the start of FAMP treatment.

Statistical considerations

To compare response to different therapies used in a sequential fashion we used the McNemar test which makes it possible to utilize each patient as his or her own control. Survival and time to progression (TTP) curves were plotted according to the

Table 2. Response to FAMP in 57 B-CLL patients previously treated with CLB and a CHOP-like regimen according to prognostic groups.

		Response to FAMP (4 courses)		
		CR+PR (%)	p	NR (%)
No. of patients	57	33 (57.8)		24 (42.1)
Age				
<55 yrs.	18	1CR+8PR (50)		9 (50)
>55 yrs.	39	2CR+22PR (61.5)		15 (38.4)
Prognostic groups				
intermediate risk	27	2CR+17PR (70.3)	0.04	8 (29.6)
high risk	30	1CR+13PR (46.6)		16 (53.3)

FAMP: fludarabine; B-CLL: B-chronic lymphocytic leukemia; CLB: chlorambucil; CHOP: cyclophosphamide. doxorubicin. vincristine. prednisone; CR: complete remission; PR: partial remission; NR: non-responders.

Table 3. Response to FAMP in 57 B-CLL patients previously treated with CLB and a CHOP-like regimen according to prior treatment status.

		Response to FAMP (4 courses)	
		CR+PR (%)	NR (%)
No. of patients	57	33 (57.8)	24 (42.1)
Pre-FAMP status			
Relapse	24	2CR+15PR (70.8)	7 (29.1)
Non-responder	33	1CR+14PR (45.4)	18 (54.5)
Transformation			
"morphologyc progression"	13	2PR (15.3)	11 (84.6)
prolymphocytoid	2		2 (100)
Richter's syndrome	2		2 (100)

FAMP: fludarabine; B-CLL: B-chronic lymphocytic leukemia; CLB: chlorambucil; CHOP: cyclophosphamide. doxorubicin. vincristine. prednisone; CR: complete remission; PR: partial remission; NR: non-responders.

Kaplan-Meier method. Survival intervals were measured from diagnosis to death from any cause. TTP was measured from the start of FAMP therapy to the detection of relapse from CR. TTP in patients with PR was calculated at the occurrence of a > 50% increase in size of masses, development of anemia and/or thrombocytopenia, or increase of lymphocyte count >10^9/L.

Analysis of survival by tumor response was carried out using the landmark method. Those patients still on study at the landmark time (fixed at the end of the 4th cycle generally corresponding to the 4th month) were separated into two response categories according to whether they had responded before that time or not.

Results

Of 57 patients who were evaluated for response, 3 (5.2%) achieved a CR, 30 (52.6%) had a PR and the remaining 24 (42.1%) failed to respond to the therapy (Table 2).

The response reflected neither the age of the patients (Table 2), nor the pattern of response to previous therapies (Table 3). In contrast, 27 patients belonging to the intermediate risk group were more likely to obtain a response to FAMP in comparison to 30 patients belonging to the high risk category (overall response, 70.3% vs. 46.6%; $p = 0.04$) (Table 2).

Morphologic changes leading to a definition of atypical B-CLL were observed at the start of FAMP therapy in 13 out of 57 (22.8%) patients. In detail, only 2 (15.3%) responded to FAMP. No response was observed in two patients with prolymphocytoid transformation and in 2 with Richter's syndrome (Table 3).

Given the homogeneous sequence of therapy used, our series was considered suitable for comparing the pattern of response to different therapies. Among the 37 patients resistant to CLB, the response rate was 40.3% with FAMP ($p = 0.037$) (Table 4) and only 17.5% with CHOP ($p = 1.0$) (Table 5). When a comparison was performed directly between CHOP and FAMP, a trend towards a significantly better response with FAMP was observed. Among 35 patients resistant to a CHOP-like regimen, the response rate was 29.8% ($p = 0.066$) after FAMP therapy (Table 6).

After a median follow-up of 13 months (range 1-65), 22 out 57 patients (38.5%) had died; overall median survival from the start of FAMP treatment was 30 months. Regarding the causes of death, death from CLL occurred in 18/22 (82%) patients (CLL progression in 17 cases and cerebral hemorrhage related to severe thrombocytopenia in 1 case). The causes of death in the other patients were: second neoplasia in 2 cases, gastrointestinal hemorrhage from esophageal varices and cardiac infarct in 1 case each.

Survival by tumor response assessed according to the landmark method after setting the cut-off time as 4 months did not show any difference in terms of overall survival between responders (median survival, 40 months) and non-responders

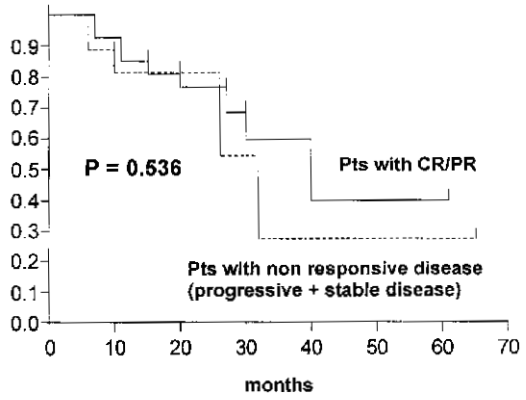

Figure 1. Evaluation of survival for patients (Pts) with CR/PR versus patients with non-responsive disease (progressive + stable disease) using the landmark method (landmark at 4 months).

(median survival, 32 months) [p = 0.536; hazard risk (HR) 0.713, 95% confidence interval (CI) 0.211-2.245] (Figure 1). The outcome of patients with progressive disease was significantly worse, comparing their survival with that of all other patients included in our study who achieved a remission (CR + PR) or kept in stable disease (p = 0.05; HR 0.367, 95% CI 0.058-1.030) (Figure 2).

In the end, TTP closely reflected the sensitivity to previous therapies. Median TTP was 12 months for 24 patients who had relapsed disease at the start of FAMP therapy and 3.5 months for 9 patients resistant to previous treatments.

Toxicity was evaluated after 231 courses of FAMP. As detailed in Table 7 myelosuppression was common during treatment. Myelosuppression was not cumulative, as the incidence of granulocytopenia and thrombocytopenia did not change as a function of courses of FAMP. In a total of 231 courses the incidence of infections or fever of unknown origin was 14.2% (4% minor infections, grade 1 World Health Organization (WHO); 4.6 % moderate, grade 2 WHO; 5.6 % major, grade 3). The major infections, described as pneumonia, were correlated with advanced stage. No patient developed autoimmune complications.

No other toxic effects were prominent. Nausea was uncommon as was stomatitis and diarrhea. Alopecia did not occur. Neurologic symptoms were uncommon.

Table 4. Comparison between pattern of response to CLB and FAMP in the same series of B-CLL patients using the Mc Nemar test.

	FAMP	
	R (%)	*NR (%)*
CLB (57 pts)		
R 20	10 (17.5)	10 (17.5)
NR 37	23 (40.3)	14 (24.5)

Chi-square = 4.364; degree freedom = 1; p = 0.037; CLB: chlorambucil; FAMP: fludarabine; B-CLL: B-chronic lymphocytic leukemia; R: responders; NR: non-responders.

Discussion

FAMP has proved to be a highly effective second-line agent for monotherapy of CLL in numerous clinical trials and following treatment response rates to FAMP ranging between 20 and 60% have been reported.[3] Variability in results might have reflected an inter-trial variation in stage of disease, treatment schedule and patients' previous treatments.

In keeping with literature results, this study demonstrates that treatment with FAMP is associated with a major cytoreductive response in more than half of previously treated patients with CLL. Although the risk of complications such as acute myelotoxicity and possible long-lasting immunosuppression caused by a reduction of $CD4^+$ cells should be considered, the profile of tolerance we observed was favorable.

In contrast to published reports,[22,23] in our CLL series no patients developed autoimmune complications. This is probably due to the selection of cases from different institutions according to a homogeneous sequence of therapy and not on the basis of FAMP therapy.

Statistical models to identify the hazard for survival and probability of response were developed from the data on patients receiving FAMP as second-line therapy.[11,12] The characteristics more strongly associated with response were hemoglobin level, serum albumin and the number of prior therapies. According to our experience, response to FAMP was closely associated with the extent of disease. So the rate of response was higher in patients belonging to the intermediate risk group than in those in the high-risk category. In contrast, the pattern of response to previous therapies did not predict response to FAMP. As a matter of fact, a significant number of patients resistant to either CLB or CHOP regimens did respond to FAMP.

Table 5. Comparison between pattern of response to CLB and CHOP-like regimen in the same series of B-CLL patients using the Mc Nemar test.

	CHOP-like regimen	
	R (%)	*NR (%)*
CLB 57 pts		
R 20	11 (19.2)	9 (15.7)
NR 37	10 (17.5)	27 (47.3)

Chi-square = 0.000; degree of freedom = 1; p = 1.000 ; CLB: chlorambucil; B-CLL: B-chronic lymphocytic leukemia; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; R: responders; NR: non-responders.

Table 6. Comparison between pattern of response to a CHOP-like regimen and FAMP in the same series of B-CLL patients using the Mc Nemar test.

	CHOP-like regimen	
	R (%)	*NR (%)*
CHOP-like 57 pts		
R 22	15 (26.3)	7 (12.2)
NR 35	17 (29.8)	18 (31.5)

Chi-square = 3.375; degree of freedom = 1; p = 0.066; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; FAMP: fludarabine; R: responders; NR: non-responders.

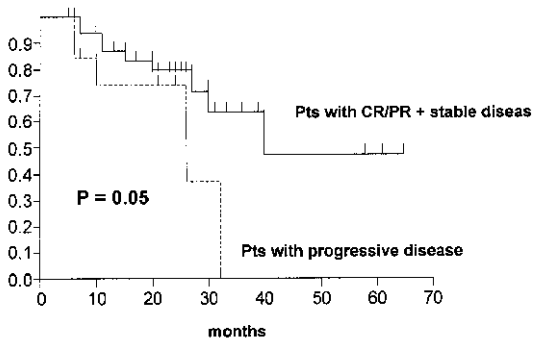

Figure 2. Evaluation of survival for patients (Pts) with CR/PR + stable disease versus patients with progressive disease using the landmark method (landmark at 4 months).

Table 7. FAMP 3rd line: toxicity and side effects [No. (%) of adverse events/321 courses].

		WHO grading			
		1	*2*	*3*	*4*
Anemia	32 (9.8)	3 (0.9)	15 (4.6)	10 (3.1)	4 (1.2)
Granulocytopenia	48 (17.8)	8 (2.4)	22 (6.8)	11 (3.4)	7 (5.2)
Thrombocytopenia	46 (14.2)	10 (3.1)	14 (4.3)	11 (3.4)	11 (3.4)
Infection	46 (14.2)	13 (4.0)	15 (4.6)	18 (5.6)	0
Gastrointestinal	25 (7.7)	22 (6.8)	3 (0.9)	0	0
Peripheral neuropathy	19 (5.8)	14 (4.3)	4 (1.2)	0	1 (0.3)
Cardiac	5 (1.5)	4 (1.2)	1 (0.3)	0	0
Lung disorders	5 (1.5)	2 (0.6)	2 (0.6)	1 (0.3)	0
Skin disorders	5 (1.5)	2 (0.6)	3 (0.9)	0	0

FAMP: fludarabine.

In comparison to other published reports dealing with the use of FAMP as salvage therapy for CLL patients, the present study assessing patients who sequentially received CLB, an anthracycline-containing regimen and finally FAMP, allows a direct comparison between these different chemotherapeutic approaches. Among patients resistant to CLB, 40.3% responded to FAMP while only 17.5% achieved a response to CHOP or CHOP-like regimens. Interestingly, the efficacy of FAMP was also confirmed when it was utilized after failure of an anthracycline-containing regimen.

With a median follow-up of 13 months (range 1-65 months) and TTP of 12 months, the overall median survival of the present series was 32 months.

The median survival of B-CLL patients receiving FAMP as second-line therapy is considerably different in various literature series, mainly reflecting either response to previous chemotherapy or time elapsing from diagnosis. In our study, evaluating survival by tumor response we used the landmark method which removes the bias due to the time between the start of therapy and response. As survival is strongly associated with response to treatment, the median survival would not be expected to improve when almost half of the patients achieved only a partial response. The low rate of CR (5.3%) in our study and the short duration of PR followed by disease progression in some patients may account, at least in part, for the relatively limited impact of the response on survival. The survival of the patients with non-responsive disease was poor.

A direct comparison between FAMP and a CHOP-like regimen was performed in a prospective mul-

ticenter, randomized study.[15] In second-line therapy, FAMP induced significantly higher rates of complete and partial remissions although this did not translate into longer remission duration or survival.[12] Our study provides further evidence that FAMP is more active than anthracycline-containing regimens. As a consequence, the use of FAMP after CLB failure appears to be mandatory.

In conclusion, FAMP is a useful tool for improving the outlook of patients with previously treated CLL, also when used outside of clinical trials. Long-term follow-up of patients in this setting confirms the existence of a considerable disease-free survival period after response to FAMP. Whether response to FAMP might be consolidated with either biological approaches or high-dose therapies is a challenge for hematologists.

Contributions and Acknowledgments

VL conceived the study and revised the paper. SM contributed to data collection, was responsible for data evaluation, statistical analysis and revised the paper. SC was responsible for data collection and interpretation, literature analysis and wrote the manuscript. EP, CB, GB, MM, AC, PL, and GS contributed to data collection. GC revised the final version of the paper.

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Disclosures

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Manuscript processing

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Potential implications for clinical practice

Fludarabine may be effective in CLL patients resistant to either CLB and/or CHOP regimens.

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