An open-label, pilot study of fludarabine, cyclophosphamide, and alemtuzumab in relapsed/refractory patients with B-cell chronic lymphocytic leukemia

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Although combination regimens have improved outcomes over monotherapy in chronic lymphocytic leukemia (CLL), patients eventually relapse. Combined fludarabine, cyclophosphamide, and monoclonal anti-CD52 antibody alemtuzumab (FCC) provided synergistic cytotoxicity with effective clearing of minimal residual disease. This phase 2 study determined FCC efficacy and safety in relapsed/refractory CD52$^+$ B-CLL after ≥ 1 line of treatment. From January 2005 through June 2008, up to 6 courses of oral fludarabine 40 mg/m^2 per day, oral cyclophosphamide 250 mg/m^2 per day, and subcutaneous alemtuzumab (Mab-Campath) 10 mg (increased to 20 mg after first 10-patient cohort) were administered days 1 to 3 every 28 days. The primary objective was overall response rate (ORR); secondary objectives included response duration, time to disease progression, and safety and tolerability. ORR was 67% in 43 patients; 30% achieved complete response. ORR significantly improved with 1 versus ≥ 2 prior therapies (P = .018), and without versus with previous monoclonal antibody treatment (P = .003). Median progression-free survival was 24.4 months, not reached in patients achieving complete response. Median overall survival was 33.6 months. Myelosuppression was the most common adverse event, with a low percentage of cytomegalovirus reactivations and manageable infections. However, close vigilance of opportunistic infections is warranted. FCC provides effective immunotherapy in relapsed/refractory CLL, including in patients with poor-risk prognostic factors. (*Blood*. 2011;118(15): 4079-4085)

Introduction

B-cell chronic lymphocytic leukemia (B-CLL) constitutes a third of adult leukemic malignancies, with an age-adjusted incidence rate of 4.2 per 100 000 men and women per year in the United States.[1,2] Approximately 15 000 new cases of chronic lymphocytic leukemia (CLL) are diagnosed each year[1,2] in the United States, with similar rates in Europe. Patients usually respond well to initial therapy; however, progressively shorter times to relapse or progression are typical until patients eventually become refractory to treatment.

Fludarabine is an effective treatment for CLL, leading to high overall response rates (ORRs) of 60% to 80% for patients in first-line treatment and 45% to 60% in previously treated patients.[3-6] In vitro, fludarabine combined with cyclophosphamide demonstrates additive or synergistic cytotoxic effects in leukemic cells.[7,8] This cell-killing activity led to their development as a combination therapy,[9] demonstrating an improvement of patient outcomes and remission times.

Continued investigation of single-agent fludarabine versus fludarabine plus cyclophosphamide (FC) showed significantly improved response rates and progression-free survival (PFS)[10-12] in first- and second-line settings for FC combination. Despite these improvements compared with historical therapy, minimal residual disease (MRD) is detectable even in patients achieving a complete response (CR), leading to eventual relapse.

The monoclonal antibody alemtuzumab is one of several agents demonstrating evidence of the ability to eradicate MRD and affect overall survival (OS) in CLL.[13,14] Alemtuzumab targets cells positive for CD52, an antigen present in high levels on a majority of normal and malignant T- and B-cell lymphocytes, but not hematopoietic stem cells.[15-17] Single-agent alemtuzumab showed durable ORRs and CR rates in first-line (83%-87% ORR, 19%-24% CR) or relapsed or refractory (33%-34% ORR, 2%-4% CR) CLL, including in patients refractory to prior fludarabine treatment.[18-21] Alemtuzumab plus fludarabine demonstrated significant clinical activity and achievement of MRD negativity in patients refractory to either monotherapy.[22,23]

The greatest challenge in CLL is to provide a treatment regimen maintaining durable hematologic and molecular remission while overcoming potential drug resistance. This study's goal was to examine therapeutic efficacy and safety effects of combined fludarabine, cyclophosphamide, and alemtuzumab (FCC) in patients with relapsed or refractory CLL.

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Table 1. Study drug regimen and dosing schedule

Drugs	Day 1	Day 2	Day 3
Fludarabine 40 mg/m^2 oral	●	●	●
Cyclophosphamide 250 mg/m^2 oral	●	●	●
Alemtuzumab subcutaneously			
First cohort: 10 mg (10 patients)	+ ●	+ ●	+ ●
Second cohort: 20 mg	+ ●	+ ●	+ ●

Anti-infective prophylaxis included the following: acyclovir 400 mg twice a day and trimethoprim sulfamethoxazole 1000 mg every other day (administered from the beginning until 6 months after treatment end).

● indicates day of administration.

Methods

This was a single-arm, open-label phase 2 study of the combination oral fludarabine, oral cyclophosphamide, and subcutaneous alemtuzumab for patients with refractory or relapsed B-CLL after ≥ 1 line of chemotherapy, including alkylating agents, purine analogs, alone or in combination, immunochemotherapy, including rituximab, or single-agent alemtuzumab. All patients provided informed written consent in accordance with the Declaration of Helsinki and the institutional guidelines of each participating site.

Patients

Male or female subjects 18 years of age and older with confirmed CD52$^+$ B-CLL (defined as peripheral lymphocyte count $> 5 \times 10^9$/L and clonal CD5, CD19, CD23, and weak SmIg$^+$ lymphocytes[24]) before study entry were included. After signed written informed consent, patients were required to have a life expectancy of ≥ 6 months, World Health Organization performance status of 0 to 2, and adequate liver and kidney function. The study included patients with relapsed disease after response, CR or partial response (PR) ≥ 6 months, or refractory disease (ie, progressive disease [PD], stable disease, or CR, PR < 6 months durable[24]) after ≥ 1 line of chemotherapy, including alkylating agents, purine analogs, alone or in combination, immunochemotherapy, including rituximab, or single-agent alemtuzumab.

Patients were excluded if they had no previous treatment with chemotherapy or immunotherapy or had received prior investigational agents, stem cell transplant, or alemtuzumab combined with chemotherapy. Also excluded were patients with fewer than 3 weeks since last treatment, HIV positivity or active viral hepatitis C or B or other active infection, or autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy.

Study objectives

The primary objective of the study was to determine ORR (CR or PR) after combination treatment with oral fludarabine, oral cyclophosphamide, and subcutaneous alemtuzumab. Secondary objectives included duration of response in responders, time to disease progression, and safety and tolerability.

Study design and treatment

Up to 6 courses of combination treatment were repeated every 28 days (Table 1), including oral fludarabine 40 mg/m^2 per day, oral cyclophosphamide 250 mg/m^2 per day, and subcutaneous alemtuzumab (MabCampath) 10 mg on days 1-3. According to the described schedule's safety profile, after the first cohort of 10 treated patients, the alemtuzumab dose was increased from 10-20 mg. Alemtuzumab therapy began with dose escalation (3, 10, and 20 mg) beginning 2 days before chemotherapy day 1.

Premedication included oral paracetamol 1 g and intravenous chlorphenamine 10 mg given 30-60 minutes before alemtuzumab. Tumor lysis syndrome prophylaxis with allopurinol 300 mg/d was recommended for ≥ 28 days of therapy. Anti-infective prophylaxis included acyclovir 400 mg twice daily and trimethoprim sulfamethoxazole 1000 mg every other day from treatment initiation until 6 months after treatment end. Patients with antigen-positive cytomegalovirus (CMV) received oral valganciclovir 400 mg for at least 3 weeks or 2 weeks after they became antigen negative.

The fludarabine dose may be 50% reduced for patients with creatinine clearance of 30-60 mL/min. In the event of hematologic toxicity (ie, neutrophils $< 1.0 \times 10^9$/L, platelets $< 75 \times 10^9$/L), treatment was delayed ≤ 2 weeks and doses reduced 25% for subsequent cycles; the dose was reduced another 25% (to 50% of original dose) if further grade 3 or 4 hematologic toxicity occurred. Granulocyte colony-stimulating factor was allowed per physician discretion. Alemtuzumab was not dose-reduced.

Response and survival assessments

Disease response was evaluated 2 months after treatment discontinuation. Efficacy was assessed by ORR, composed of CR and PR, as defined according to National Cancer Institute Working Group response criteria.[24] Response assessments included clinical examination, computed tomography scan of lymph node regions involved at baseline, and peripheral blood evaluation. Bone marrow biopsy confirmed the CR.

Patients with PD per clinical parameters (eg, lymphocytosis, lymphadenopathy, splenomegaly) could discontinue treatment after 2 cycles. Patients with clinical stable disease after 3 cycles could continue treatment at the investigator's discretion. In case of clinical response achievement after at least 4 cycles administered, at physician discretion, treatment could be discontinued and patients underwent disease reassessment.

MRD was assessed in patients achieving CR. Bone marrow was analyzed at the time of response evaluation; analyses via quadruple antibody detection followed the method described by Rawstron et al.[25]

Laboratory assessments

Lymphocyte immunophenotype was determined by flow cytometry using cell surface markers CD5, CD20, CD19, CD23, CD79b, FMC7, and SmIg to establish CLL diagnosis. Immunoglobulin variable heavy chain (IgVH) mutational status was examined at baseline. Genetic analyses evaluated morphology and CLL-related chromosome abnormalities del13q, trisomy 12, del11q, and del17p.

Safety

Patients were monitored before, during, and after each cycle and throughout the 4-week follow-up period for adverse events, clinical status, vital signs, and critical laboratory data. Toxicity was graded per the National Cancer Institute Common Terminology Criteria.[26] Patients were monitored for infections after each cycle and throughout the 4-week follow-up, including weekly monitoring for CMV reactivation (pp65 antigenemia) during treatment and for 6 weeks after treatment discontinuation. Patients with symptomatic CMV reactivation discontinued treatment and received oral valganciclovir. Asymptomatic cases showing positive CMV antigenemia were retested 2 days later. If the test result showed increasing positivity, treatment was discontinued and valganciclovir was administered. Treatment resumed at the physician's discretion if antigenemia cleared and symptoms resolved.

Statistical analysis

Absence of MRD was defined as CR(MRD$^-$), with no detection of neoplastic B cells by multichannel flow cytometry on bone marrow cells. Duration of response was defined for all responding patients (CR or PR) as time from date of first response assessment to date of documented progression, death from any cause, or relapse. Differences in response rate between groups were analyzed by Fisher exact test; association of continuous or discrete variables with the endpoints was measured with Wald test after logistic regression. Time to disease progression was measured from treatment initiation in responding patients to disease progression. OS was measured from treatment initiation until death. Time to retreatment in responding patients was measured from end of FCC to start of a further treatment line. Time-to-event data (time to disease progression, duration of response) and survival were analyzed using the Kaplan-Meier method. Confidence intervals for median time were calculated with nonparametric methods. Statistical significance was assumed for $P < .05$.

Table 2. Patient demographics

Demographics	N = 43
Median age, y (range)	60 (39-77)
Sex, n (%)	
Female	17 (40)
Male	26 (60)
Binet stage, n (%)	
A	1 (2)
B	24 (36)
C	18 (42)
Median time from diagnosis to FCC, mo (range)	69 (10-276)
Median time from last treatment to FCC, mo (range)	14 (1-90)
Disease status, n (%)	
Relapsed	32 (74)
Refractory	11 (26)
No. of prior treatments, n (%)	
1	10 (23)
2	20 (46)
≥ 3	13 (31)
Prior fludarabine	40 (93)
Prior alkylating agent	38 (88)
Prior monoclonal antibody	16 (37)
Fludarabine refractory*	6 (15)
IgVH status,* n (%)	
Mutated	11 (32)
Unmutated	23 (68)
ZAP-70,* n (%)	
Negative	16 (48)
Positive	17 (52)
FISH,* n (%)	
Normal or 13q deletion	15 (38)
Trisomy 12	6 (15)
11q deletion	7 (18)
17p deletion	11 (28)

FCC indicates fludarabine, cyclophosphamide, alemtuzumab.
*Data not available for all patients.

Results

Baseline demographics and clinical characteristics

From January 2005 through June 2008, 43 patients were enrolled in this phase 2 study at 10 centers in Italy. Their median age was 60 years, and 60% were male (Table 2). All but one had Binet stage B or C disease. A majority had relapsed disease (74%); 26% were refractory to prior therapy. Nearly all (93%) previously received fludarabine, including 15% refractory to fludarabine. An evaluation of IgVH mutational status performed on 34 patients showed 68% with unmutated IgVH. Approximately one-half were $ZAP70^+$ (17 of 33 patients). Fluorescence in situ hybridization analysis of 39 patients showed 46% presenting with deleted 11q or 17p.

Treatment administration

A total of 154 courses were administered, with a median of 4 (range, 1-6). Twenty-four patients received 4 or more courses of treatment, with 13 patients completing all 6 courses. Reasons for discontinuation or withdrawal before the sixth treatment cycle included response achieved (8 patients), disease progression (5 patients), symptomatic CMV reactivation (4 patients), persistent cytopenia (4 patients), major infection (4 patients), consent withdrawal (2 patients), intestinal bleeding (1 patient), pulmonary thromboembolism (1 patient), and cutaneous mycobacteriosis sustained by *Mycobacterium bovis* presenting as a single nodular lesion (1 patient).

Response

In all 43 patients, the ORR was 67%, with 30% of patients achieving CR (Table 3). A total of 14% of patients maintained stable disease, whereas 19% progressed. Pretreatment variables associated with response achievement are listed in Table 4. The ORR was significantly higher in patients receiving only one prior line of therapy (100%) compared with those receiving 2 (70%) or more (38%) prior treatments ($P = .018$). No difference in ORR was observed between patients with fludarabine-refractory disease versus patients with fludarabine-sensitive disease. In contrast, patients who received previous monoclonal antibody treatment showed a significantly inferior ORR compared with those without prior monoclonal antibody therapy (38% vs 85%, respectively; $P = .003$). Longer time from last treatment to FCC initiation indicated a significantly higher probability of attaining a response (cutoff, 21 months; $P = .018$).

No clinical or biologic variables had prognostic significance for response achievement. Moreover, no considered variables affected the attainment of CR. MRD^- CR was observed in 6 patients. Notably, all but one patient received 2 or more previous lines of therapy; all had received previous fludarabine, demonstrating treatment-sensitive disease in all cases.

Survival and time to retreatment

At a median follow-up of 16.7 months (range, 1-49.5 months), 29 patients responding to FCC had a median PFS of 24.4 months (Figure 1A). Thirteen patients in CR showed a significantly prolonged PFS (not yet reached after median follow-up of 23.3 months) compared with the 16 patients in PR (13 months), respectively ($P < .0001$; Figure 1B). None of the 6 patients with MRD^- CR relapsed after a median observation period of 25.5 months (range, 8.3-49.5 months)

Median OS time in 43 enrolled patients was 33.6 months after a median follow-up of 22 months (range, 2.1-53.8 months; Figure 1C). Median OS was prolonged, although not statistically significant, for patients in CR versus PR (45.6 vs 29.9 months, respectively; $P = .2775$; Figure 1D).

Median time to retreatment in 29 responding patients was 33.8 months. At a median follow-up of 23.3 months, median time to retreatment was significantly longer in patients achieving CR, compared with patients in PR (not yet reached vs 13.9 months, respectively; $P = .0002$).

Safety and tolerability

Myelosuppression of all grades was the most commonly reported adverse event. A third of patients demonstrated grade 3 or 4 neutropenia (Table 5). All patients received granulocyte colony-stimulating factor during treatment. Grade 3 or 4 nausea and vomiting occurred in 10% of patients, with one patient each experiencing grade 3 or 4 hypotension, diarrhea, bleeding, and

Table 3. Response after FCC in relapsed or refractory patients

Response (N = 43)	n (%)
ORR	29 (67)
CR	13 (30)
PR	16 (37)
SD	6 (14)
PD	8 (19)

FCC indicates fludarabine, cyclophosphamide, alemtuzumab; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; and PD, progressive disease.

Table 4. Percent response to FCC by disease characteristics

Patient characteristics (N = 43)	n	NCI-WG response, n (%)			
		CR (all patients)	CR (MRD⁻)	PR	ORR
All patients	43	13 (30)	6 (14)	16 (37)	29 (67)
Binet					
A	1	0	0	1 (100)	1 (100)
B	24	10 (42)	4 (17)	6 (25)	16 (67)
C	18	3 (17)	2 (11)	9 (50)	12 (67)
Disease status					
Relapse	32	10 (31)	5 (16)	12 (38)	22 (69)
Resistant	11	3 (27)	1 (9)	4 (36)	7 (63)
No. of previous treatments					
1	10	5 (50)	1 (10)	5 (50)	10 (100)†
2	20	6 (30)	4 (20)	8 (40)	14 (70)
≥ 3	13	2 (15)	1 (8)	3 (23)	5 (38)
Previous fludarabine					
Yes	40	11 (28)	6 (15)	15 (37)	26 (65)
No	3	2 (67)	0	1 (33)	3 (100)
Previous alkylating agent					
Yes	38	10 (26)	5 (13)	14 (37)	24 (63)
No	5	3 (60)	1 (20)	2 (40)	5 (100)
Previous anthracycline					
Yes	9	3 (33)	1 (11)	2 (22)	5 (55)
No	34	10 (29)	5 (15)	14 (41)	24 (70)
Previous monoclonal antibody					
Yes	16	2 (13)	2 (13)	4 (25)	6 (38)‡
No	27	11 (41)	4 (15)	12 (44)	23 (85)
Fludarabine refractory*					
Yes	6	1 (17)	0	3 (50)	4 (67)
No	34	10 (29)	6 (18)	12 (35)	22 (65)
IgVH status*					
Mutated	11	6 (55)	3 (27)	2 (18)	8 (73)
Unmutated	23	5 (22)	3 (13)	13 (57)	18 (79)
ZAP70*					
Negative	16	5 (31)	2 (13)	5 (31)	10 (62)
Positive	17	5 (29)	3 (18)	8 (47)	13 (76)
FISH*					
Normal or 13q deletion	15	6 (40)	4 (27)	6 (40)	12 (80)
Trisomy 12	6	3 (50)	0	1 (17)	4 (67)
11q deletion	7	1 (14)	0	3 (43)	4 (57)
17p deletion	11	3 (27)	2 (18)	5 (46)	8 (73)

FCC indicates fludarabine, cyclophosphamide, alemtuzumab; NCI-WG, National Cancer Institute Working Group; CR, complete response; PR, partial response; and ORR, overall response rate.

*Data not available in all patients.

†Statistically significant difference between patients treated with one prior line of therapy versus those treated with > 1 prior line of therapy ($P < .05$).

‡Statistically significant difference between patients treated with monoclonal antibodies versus no monoclonal antibodies ($P < .05$).

pulmonary embolism. Symptomatic CMV reactivation occurred in 8 cases (19%), resulting in study stoppage for 4 patients.

Major infections, defined as sepsis, pneumonia, or infection requiring hospitalization, occurred in 12 patients: 1 hepatitis B virus reactivation, 8 cases of pneumonia, and 3 of sepsis. The hepatitis B virus reactivation was in a patient showing PD. Among the 8 episodes of pneumonia, 6 were only radiologically documented. In the remaining 2 cases with primary PD, therapy was stopped because 1 had *Nocardia*, and 1 *Scedosporium*. Three episodes of sepsis were detected, sustained by *Staphylococcus* in 2 patients and *Pseudomonas aeruginosa* in the third case, leading to treatment interruption. During patient follow-up, 2 late major infections (1 pulmonary tuberculosis and 1 aspergillosis) were recorded, both in patients with CR after the end of treatment.

Statistical analysis showed that ZAP-70 negativity was the only variable significantly predictive of major infections ($P = .037$). A strong trend toward developing infections was observed in patients with 11q positivity ($P = .056$) and previous alkylating agent therapy ($P = .056$). In 29 responding patients, 8 observed deaths were related to disease progression in 5 patients, Richter syndrome in 2, and late pulmonary tuberculosis in 1. Among nonresponding patients, 11 deaths were recorded and were the result of PD in 10 patients and pneumonia in 1 patient.

Grade 1 or 2 adverse events related to subcutaneous alemtuzumab administration included skin reactions in 43 courses (28%), fever in 39 courses (25%), and hypotension in one course. As previously reported, one case of grade 3 or 4 hypotension was observed. More than one-third of skin reactions (37%) and fever (44%) were experienced during the first therapy cycle.

Discussion

Superiority in number of responses and PFS after combined fludarabine and cyclophosphamide, compared with single-agent fludarabine, has been confirmed by numerous phase 3 trials in

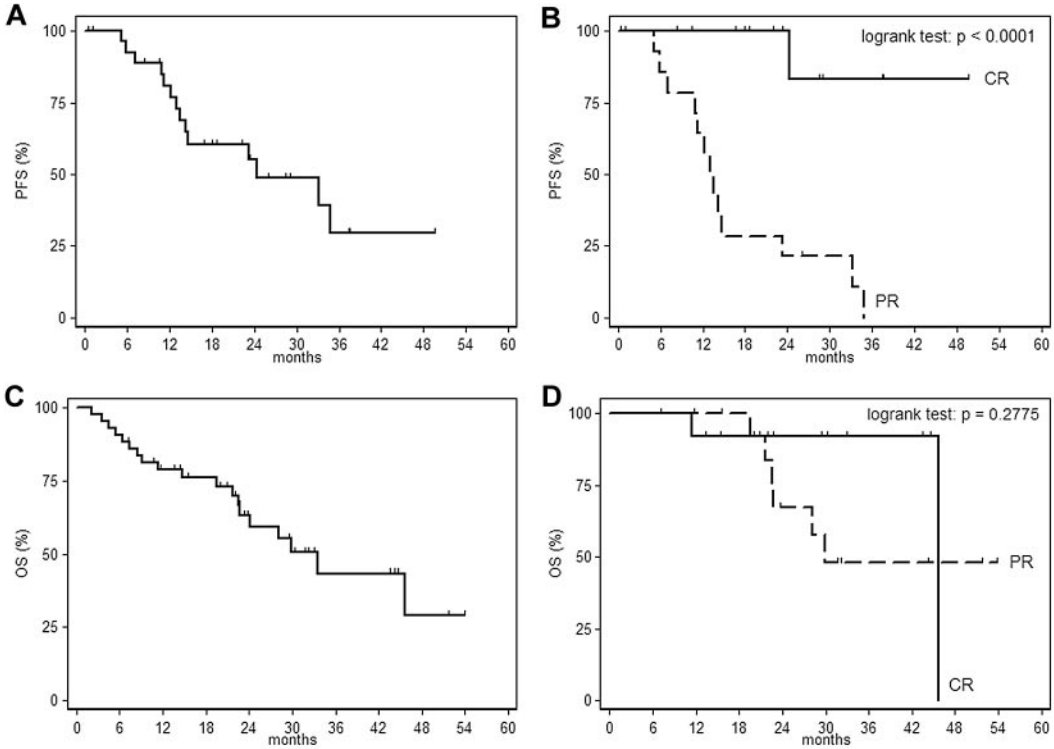

Figure 1. PFS and OS of patients receiving FCC. (A) PFS in responders. (B) PFS according to response (CR vs PR). (C) OS in all 43 enrolled patients. (D) OS in responders.

CLL.[10-12] Alemtuzumab induces a response in relapsed or refractory disease, although patients with bulky lymphadenopathy usually do not respond to therapy.[14] However, alemtuzumab plus fludarabine showed increased response rates compared with either single agent[22] and represents a promising chemoimmunotherapeutic approach with an acceptable toxicity profile.[23]

Table 5. Grade 3 or 4 adverse events with FCC (154 courses; N = 43)

Adverse events*	Grade 3/4 adverse events
Hematologic, n (% of cycles)	
Neutropenia†	71 (46)
Anemia	13 (8)
Thrombocytopenia	18 (12)
Nonhematologic, n (% of cycles)	
Hypotension	1 (0.6)
Nausea and vomiting	15 (10)
Diarrhea	1 (0.6)
Bleeding	1 (0.6)
Pulmonary embolism	1 (0.6)
Infections	
Major infections, no. of episodes	12
Pneumonia	8
Radiologically documented	6
Nocardia	1
Scedosporium	1
Sepsis	3
Staphylococcus aureus	2
Pseudomonas aeruginosa	1
HBV reactivation	1
Symptomatic CMV reactivation‡	8

FCC indicates fludarabine, cyclophosphamide, alemtuzumab.
*Median number of cycles = 4 (range, 1-6).
†Granulocyte colony-stimulating factor administered for 117 cycles (76%).
‡No CMV disease

The study's major limitation was that biologic risk factors (IgVH, fluorescence in situ hybridization, and ZAP70) were not determined. Poor prognostic factors were strongly represented in our series, including 68% unmutated IgVH and 46% del17p or del11q. Importantly, after FCC treatment, response achievement was independent of mutational status or cytogenetics; ORR was 79% in patients with unmutated IgVH and 67% in patients with del17p or del11q. These data are similar to the results from the Badoux et al phase 2 trial of fludarabine, cyclophosphamide, and the anti-CD20 monoclonal antibody rituximab (FCR) in patients with unfavorable prognostic features.[27]

However, in our series, patients carrying del 17p showed higher ORR (73%) compared with those reported in the Badoux et al series (ORR = 35%).[27] Recently, efficacy data for FCR in a phase 3 trial (REACH trial) in pretreated CLL showed responses similar to those observed in our study.[28] However, eligibility criteria in the FCR study allowed patients with only one previous line of treatment.[28] In our series, the median number of previous treatments was 2, with one-third of patients treated with ≥ 3 previous treatments. Fludarabine was the preceding therapy in 40 patients (93%) here, compared with 18% in the FCR study.[28] The heavily pretreated history of our patients may explain their shorter median PFS, compared with REACH trial patients (24.4 vs 30.6 months, respectively).[28] Interestingly, the PFS values after FCR in the Badoux et al[27] series were similar to those in our study, given comparable patient characteristics. Moreover, median PFS values after FCC compare favorably with those reported by Elter et al,[23] using the same combination without cyclophosphamide and a higher alemtuzumab dose. In addition, among our patients who achieved a CR, 83% showed a persistent response after a median follow-up of 23.3 months. The increasing importance conferred to MRD eradication in patient outcomes has been confirmed in the

6 patients who reached an MRD$^-$ status because none progressed after a median follow-up 25.5 months.

Disease status at the time of FCC treatment had no impact on efficacy among the patients resistant to, compared with those having disease sensitive to, last treatment. Even the quality of their responses was similar (CR: 31% vs 27%).

As previously reported, subcutaneous alemtuzumab demonstrated at least equivalent efficacy compared with intravenous alemtuzumab with reduced adverse events.[19] In our experience, the subcutaneous regimen was well tolerated. Skin reactions at the injection site were mild. Myelosuppression is commonly the most frequent toxicity in these studies. In the present study, grade 3 or 4 neutropenia was detected in 46% of courses; this is comparable with other studies of previously treated patients with chemoimmunotherapeutic regimens.[27,28]

A major concern is the low percentage of patients who completed the expected 6 courses of treatment. However, the reason for halting therapy before the planned 6 cycles in 8 cases was the achievement of response in fewer treatment cycles. Furthermore, in our series, more than one-half of the patients (16 of 29) showing an objective response had been treated with < 6 courses. This may lead to the speculation that, when planning treatment with this combination, a lower number of courses should be considered.

A higher number of major infections were recorded in our series if compared with those developing after FCR in the M. D. Anderson Cancer Center trial.[27] However, most of the major infections observed in our patients were manageable with only 2 sustained by opportunistic agents. The infection rate was not influenced by the dose per cycle of alemtuzumab administered in the 2 cohorts (30 mg alemtuzumab/cycle vs 60 mg alemtuzumab/cycle).

Finally, the percentage of symptomatic CMV reactivations was low. A close vigilance of opportunistic infections and a risk-adjusted anti-infective prophylaxis is strongly recommended with this treatment combination. Because of the heavily pretreated nature and poor genetic profiles of these patients, the rate of treatment-associated death was deemed acceptable, with 2 deaths related to infections, one occurring during follow-up.

Although high response rates have been achieved, ongoing experiences with this combination in the first-line setting has led to some safety challenges. A study by the French group comparing first-line FC plus MabCampath versus FCR was prematurely terminated because of an elevated number of deaths and safety concerns in the FC plus MabCampath arm.[29] Preliminary results of the first-line FC plus MabCampath (low-dose alemtuzumab) versus FC (HOVON study) suggest an increased risk of infections in the FC plus MabCampath arm.[30]

Based on these study results, it is our opinion that the use of the FCC combination is recommended in selected relapsed or refractory patients, such as those showing unmutated IgVH status, and high-risk genetic abnormalities.

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Authorship

Contribution: M.M. was the principal investigator and was involved in the conception and design; V.B.P., F.R., P.S., F.I., I.A., and E.V. collected and assembled the data; A.T., M.C., M.S., L.U., A.D.B., A.Z., and E.M. performed data analysis and interpretation; M.M., F.R., M.C., M.S., P.S., F.I., L.U., I.A., E.V., A.D.B., A.Z., and E.M. were involved in writing the manuscript; M.M., A.T., V.B.P., F.R., M.C., M.S., F.I., L.U., E.V., A.D.B., A.Z., and E.M. provided study materials or patients; and all authors gave final approval.

Conflict-of-interest disclosure: M.M. has had a consultancy or advisory role with and has received honoraria from Schering, Bayer, and Genzyme. The remaining authors declare no competing financial interests.

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