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PHASE III STUDIES

A Phase III trial of fludarabine, cyclophosphamide, and rituximab vs. pentostatin, cyclophosphamide, and rituximab in B-cell chronic lymphocytic leukemia

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Summary *Background* Uncontrolled studies comparing pentostatin (P), cyclophosphamide (C), and rituximab (R) (PCR) to fludarabine plus C+R (FCR) suggest similar efficacy with fewer infectious complications with PCR. We compared FCR and PCR in previously-untreated or minimally-treated B-cell chronic lymphocytic leukemia (CLL). *Treatment* FCR (F 20 mg/m^2 Days 1–5, C 600 mg/m^2 Day 1, R 375 mg/m^2 Day 1) (28-day cycles) or PCR (P 4 mg/m^2 Day 1, C 600 mg/m^2 Day 1, R 375 mg/m^2 Day 1) (21-day cycles). Dose 1 of R: 100 mg/m^2 was given on Day 8 Cycle 1 and the remainder on Day 9; in subsequent cycles the entire dose was given on Day 1. *Results* Ninety-two patients were randomly assigned to each group (N=184). Groups were balanced; ~20% had received prior chemotherapy. The infection rate (FCR/PCR) was 31%/36%, the infective event rate was 38%/45%; 30 (35%)/37 (44%) patients were hospitalized; total hospitalization days was 271/404. 12 (14%)/6 (7%) patients achieved complete remissions (CR); the overall response rate (ORR) including CR+nodular PR (nPR)+PR was 59%/49%. Grade 3–4 treatment related AEs: neutropenia (69%/57%), leukopenia (34%/17%), thrombocytopenia (13%/6%). Grade 3–4 infections: febrile neutropenia (8%/6%), fever (2%/6%), infection (1%/3%), urinary tract infection (1%/0%), pneumonia (3%/1%), and sepsis (1%/2%); 5 deaths (1 FCR/4 PCR) were treatment-related. *Conclusions* PCR and FCR have significant activity in CLL and can be given safely in the community setting despite significant toxicity. ORRs were lower than expected; the CR rate was higher (NS) with FCR. This trial did not demonstrate a lower infection rate with PCR.

Keywords Chemotherapy · Community-based · Comparative · Infection · Leukemia

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Introduction

Although some patients with chronic lymphocytic leukemia (CLL) will never require therapy, most will ultimately

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require treatment and many will die of their disease. For many years the standard approach to CLL therapy centered on the use of oral alkylating agents such as chlorambucil, either alone or in combination with steroids.

Chlorambucil often produces responses in CLL, but complete remissions are rare, and the impact on the natural history of the disease is minimal. The development of purine analogues changed the standard approach to CLL. Complete responses were more common, and response rates were much higher than seen previously [1]. A multicenter randomized trial comparing fludarabine with chlorambucil as initial treatment of CLL demonstrated that fludarabine yields higher response rates, duration of remission, and progression-free survival (PFS). In early reports prior to the conduct of this study, overall survival (OS) was not significantly improved by fludarabine, possibly because of the high frequency of subsequent crossover to fludarabine in the chlorambucil-treated patients [2]. However, more recent studies have shown that OS was improved [3].

Combinations of fludarabine and alkylating agents have been evaluated. The combination of fludarabine and chlorambucil did not improve responses compared with fludarabine alone, and had unacceptable toxicity [2]. The combination of fludarabine and cyclophosphamide (FC) was more successful, with response rates over 80%, including a 38% response rate in patients refractory to fludarabine. Although the CR rate for FC was not increased compared with historical controls treated with fludarabine alone, minimal residual disease was less common in patients treated with FC initially, and response duration appeared to be significantly prolonged [4].

The anti-cd20 humanized antibody rituximab had disappointing single agent activity in CLL [5]. Rituximab was evaluated in combination with fludarabine (FR) by the Cancer and Leukemia Group B (CALGB) [6]. Results of therapy were compared retrospectively to a previous CALGB trial of fludarabine. PFS and OS were both statistically significantly better for FR.

The combination of fludarabine, cyclophosphamide, and rituximab (FCR) was evaluated in 177 previously treated patients with CLL [7]. Overall response rate was 73%, with a CR rate of 25%. Molecular remissions were seen in a third of patients achieving CR. Results were better with FCR as initial therapy, with a 70% CR rate, and an overall response rate of 95% [8]. A subsequent report of 300 patients updated the results with median time to progression of 80 months, and 6-year overall survival of 77% and PFS 51% [9]. Hematologic and infectious toxicities were prominent with this regimen, and results in patients over the age of 70 were disappointing compared to younger patients.

Pentostatin-based combinations were evaluated in a similar fashion. Although the single agent activity of pentostatin appears less than that of fludarabine [10, 11], it was postulated that the lower incidence of myelosuppression with pentostatin might make it a better agent in combination therapy of CLL [12]. The combination of pentostatin and cyclophosphamide (PC) was studied in 23 patients with previously treated CLL [12]. There were 17 responses (RR 74%) including 4 CRs. Subsequently the combination of pentostatin, cyclophosphamide, and rituximab was evaluated in previously untreated CLL. Responses were seen in 91% of patients, with 41% CRs. In contrast to the results with FCR, patients above and below the age of 70 did equally well. Hematologic toxicity was common (58%, Grade 3) but infectious complications appeared less frequent than previously reported with FCR [13, 14].

This multicenter, community-based trial compared FCR with PCR in previously-untreated or minimally-treated CLL. Primary endpoints were infectious events and complications, with secondary endpoints of efficacy. The operating hypothesis was that PCR might offer equal efficacy to FCR with less toxicity.

Patients and methods

Study design

This was a Phase III, open label, randomized study. Patients were randomized centrally into 1 of 2 treatment arms: Arm 1 (FCR) or Arm 2 (PCR); 140 patients/arm was the enrollment goal.

Patients

Eligible patients ≥18 years of age, who had progressive, histologically confirmed, CD20+, B-cell CLL were included in this trial. Patients may have received 1 prior course of chemotherapy, including rituximab or fludarabine; prior radiation was not allowed. Other inclusion criteria included ECOG 0–2, normal renal function, adequate bone marrow and hepatic function.

Patients were excluded if they had small lymphocytic lymphoma in nodes without lymphocytosis, received >1 prior treatment regimen, received any prior radiation or pentostatin, were CD20 negative, had calculated creatinine clearance <41 mL/min if the serum creatinine was ≥1.5 mg/dL, were pregnant or breastfeeding, were known to be HIV positive, had uncontrolled thyroid disease or a history of recent unstable organic heart disease (or stable organic heart disease with LVEF <50%), had autoimmune hemolytic anemia, was known to be sensitive to any of the study drugs or any component thereof, or was otherwise unable to comply with the requirements of the study.

Treatment

Arm 1 (FCR) consisted of F 20 mg/m^2 Day 1–5, C 600 mg/m^2 Day 1, and R 375 mg/m^2 Day 1 in 28-day cycles. Arm 2 (PCR) was P 4 mg/m^2 Day 1, C 600 mg/m^2 Day 1, and R 375 mg/m^2 Day 1 in 21-day cycles. In both treatment groups, the first dose of R was split in Cycle 1 (100 mg/m^2 given on Day 8 and the remainder of the 375 mg/m^2 dose on Day 9); in subsequent cycles the entire 375 mg/m^2 R dose was given on Day 1. Arm 1 patients were treated up to a maximum of 6 cycles; Arm 2 was limited to a maximum of 8 cycles. Patients in both arms were treated to the maximum number of cycles or until confirmation of complete response, progressive disease, or intolerable toxicity. All patients received viral infection prophylaxis.

The protocol was approved by a central Institutional Review Board with jurisdiction over specific sites that registered patients on study, and all patients were required to sign an informed consent form before being enrolled into the study.

Assessments

Patients were assessed for toxicity at each clinic visit. Brief physical exams, complete blood counts, and complete metabolic profiles were done prior to the start of every cycle and radiographic assessments of disease were done every 3 cycles. PCR patients were also assessed prior to Cycle 8.

Criteria for assessing response and toxicity

Responses were evaluated using guidelines established by the National Cancer Institute-Sponsored Working Group for Chronic Lymphocytic Leukemia [15]. Assessment of disease included physical examination(s) and evaluation(s) of peripheral blood and bone marrow. Confirmatory assessments were done at intervals not less than 8 weeks following prior determination of response.

Toxicities and adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 [16]. Adverse events were recorded from the start of treatment and for up to 30 days following the last dose of study drug.

Statistical analysis

The primary objective of this study was to compare the infection rates between the 2 treatment arms. Using χ^2 test in NQuery, with a predetermined 2-sided significance level α=0.05 and a desired power of 90%, a sample size of 128 patients/arm was sufficient to detect a 20% difference of percentages of patients with infection (40%–44% for PCR vs. 60%–64%). Randomization was conducted centrally at a 1:1 ratio as planned.

Three (3) types of "infection rate" were defined for this analysis: percentage of patients with infection, number of infections/cycle, and ratio of number of infections vs. number of febrile events. Based on the per-protocol population, these infection rates were calculated for both treatment arms. 95% confidence intervals (CI) were provided using the exact binomial method and t approximation; χ^2 test and Wilcoxon rank-sum test were conducted for between-arm comparison.

Descriptive statistics of 2-month (8~10 weeks) post-treatment ANC, platelet, and hemoglobin values were provided with 95% CI as well as hematology recovery rate.

Response using guidelines of the National Cancer Institute-Sponsored Working Group for Chronic Lymphocytic Leukemia, was classified by 6 categories: complete remission (CR), nodular PR (nPR), partial remission (PR), stable disease (SD), progressive disease (PD) and "not evaluable" (NE). Frequencies and rates were calculated for each of the 6 categories with 95% CI provided, using exact binomial method for both arms. CR, nPR, or PR were considered as responses.

In the per-protocol population the Kaplan-Meier [17] method was used for OS and PFS and the log-rank test was provided to calculate the differences between the curves.

Drug administration and adverse events were used to assess safety issues. Cycle numbers, administered dosage (cumulative dose, median dose, and dose intensity by different study drugs), and dose modification information were assessed in frequency table and/or descriptive statistics. All treatment-related adverse events, with severity graded, were tabulated by term and maximum grade. All these assessment were based on safety population.

Results

Patient characteristics

A total of 184 patients were registered between January 2004 and November 2007. Registration was stopped prematurely as the study sponsor decided not to pursue the indication of CLL for pentostatin.

At baseline, both treatment arms were well balanced for sex, race, age, and proportion previously untreated. Slightly more patients in the FCR arm were stage III and ECOG 0. Patient demographics are summarized in Table 1. Overall, all patients were followed for a median of 30.5 months and 29.0 months, for FCR and PCR, respectively.

At least 50% of patients in each treatment arm completed the treatment portion of the study. Toxicities were the most frequent reason for patients discontinuing study treatment.

Table 1 Baseline demographics

	FCR *N*=92 n (%)	PCR *N*=92 n (%)
Sex		
Female	27 (29.3)	22 (23.9)
Male	65 (70.7)	70 (76.1)
Race		
White	81 (88.0)	84 (91.3)
Black	7 (7.6)	5 (5.4)
Hispanic	2 (2.2)	3 (3.3)
Other	2 (2.2)	0
Age (years)		
Median (range)	63.6 (31.9–81.2)	64.1 (36.0–84.4)
Patients >70 year of age	26 (28.3)	23 (25.0)
Stage at diagnosis		
0	29 (31.5)	28 (30.4)
I	29 (31.5)	24 (26.1)
II	18 (19.6)	21 (22.8)
III	4 (4.3)	11 (12.0)
IV	9 (9.8)	5 (5.4)
Unknown	3 (3.3)	3 (3.3)
Stage at baseline		
I	5 (5.4)	5 (5.4)
II	38 (41.3)	51 (55.4)
III	20 (21.7)	16 (17.4)
IV	28 (30.4)	19 (20.7)
Unknown	1 (1.1)	1 (1.1)
ECOG performance status		
0	70 (76.1)	59 (64.1)
1	21 (22.8)	31 (33.7)
2	1 (1.1)	2 (2.2)
Prior therapy		
Chemotherapy	19 (20.7)	21 (22.8)

Treatment outcomes

Using a per-protocol analysis, CRs were achieved by twice as many FCR patients as PCR patients (14 vs 7, [*P*=0.14]); PR (42% and 39%) and nodular PRs (3% and 4%) were similar between groups and stabilization of disease (SDs) were achieved by 30% of FCR patients and 45% of PCR patients. No PCR patient experienced disease progression as best response; however, 3 FCR patients (3%) did. Some patients (7% FCR and 6% PCR) had no assessment of efficacy beyond their baseline assessment. These patients were deemed not evaluable (6 [7%] FCR and 5 [6%] PCR patients). There were no differences in response rate, calculated as CR+nPR+PR, between the 2 treatment groups (p=0.87). Time to response was 4.1 and 5.0 months, respectively, and the median duration of response in these patients has not yet been achieved; however the range was 7.3 to 29.6 months for FCR and 2.8 to 30.1 months for PCR

For patients who had received no prior treatment (treatment naïve), results were similar to what was reported above. CRs were still twice as frequent in the FCR group (16% vs 8%), PR (43% vs 41%) and nodular PRs (3% vs 2%) were similar between groups and stabilization of disease (SDs) were achieved by 28% of FCR patients and 42% of PCR patients. There were no differences in response rate, calculated as CR +nPR+PR, between the 2 treatment groups (p=0.17). Time to response was 3.9 and 4.2 months, respectively, and the median duration of response in these patients has not yet been achieved; however the range was 3.1 to 30.2 months for FCR and 2.4 to 30.2 months for PCR.

Endpoints including responses, time to and duration of response, hematologic recovery, post treatment ANC, infective rate, hospitalizations, hospitalization days, and reasons for discontinuation are included in Table 2. There was a trend towards increased platelet, hemoglobin, and ANC recovery (ANC at the time of next cycle) in the PCR group. PCR patients experienced more infections/cycles and there were 38 PCR patients with a total of 131 infective events (37 patients with 54 hospitalizations) compared to 33 FCR patients with 80 infective events (30 patients with 43 hospitalizations). Even though PCR patients had an increased rate of infective events that included more hospitalizations, they actually had slightly fewer hospitalizations/cycle spread across 8 cycles of PCR vs 6 cycles of FCR. Median time to first response was ~3 months in each group and the median duration of response was 26.4 and 24.3 months respectively.

The median OS for FCR and PCR has not been reached after 32 months. 12-month OS was 90.4% and 90.5% and 24-month OS was 86.7% and 79.1% for the FCR and PCR groups, respectively. Similarly, the median PFS has not been reached for either group. 12-month PFS was 85.9% and 83.8% and 24-month PFS was 72.0% and 62.9% for the FCR and PCR groups, respectively. OS and PFS are summarized graphically in Fig. 1.

For patients older than 70 years, responses were similar in the 2 treatment arms; ~9% achieved CR in each arm; the CR+nPR+PR rate was 43% and 50%, respectively. Nine (9)/23 FCR (39%) and 11/22 PCR patients (50%) had at least 1 infection; both groups had a median of 0 infections/cycle (mean 0.23 and 0.24, respectively). The median infection rate (number of infection/febrile events) was 1.0 in both groups of older patients. For FCR, the median OS has not been reached; 12-month OS was 72% and 24-month OS was 67%; for PCR the median OS was not been reached and 12- and 24-month OS was 95% and 72%, respectively. Median PFS was 27.8 months for FCR; 12- and 24-month PFS was 64% and 54%, respectively. For PCR the median PFS has not been reached and 12- and 24-month PFS was 85% and 59%, respectively. None of the

Table 2 Treatment outcome

	FCR	PCR
Total number enrolled	92	92
Total number treated	88	89
Evaluable patients per protocol	86	85
Best response	n (%) [95% CI]	n (%) [95% CI]
CR	12 (14.0) [7.4, 23.1]	6 (7.1) [2.6, 14.7]
P-value	0.14	
nPR	3 (3.5) [0.7, 9.9]	3 (3.5) [0.7, 10.0]
PR	36 (41.9) [31.3, 53.0]	33 (38.8) [28.4, 50.0]
SD	26 (30.2) [20.8, 41.1]	38 (44.7) [33.9, 55.9]
PD	3 (3.5) [0.7, 9.9]	0
NE[a]	6 (7.0) [2.6, 14.6]	5 (5.9) [1.9, 13.2]
Overall response (CR+PR+nPR)	51 (59.3) [48.2, 69.8]	42 (49.4) [38.4, 60.5]
P-value	0.19	
Time to response (months)		
Median (range)	2.8 (1.8–11.5)	3.2 (1.4–20.4)
P-value	0.20	
Duration of response (months)		
Median (range)	26.4 (3.1–30.2)	24.3 (2.4–30.2)
P-value	0.36	
Hematologic recovery[b]	n (%)	n (%)
Patients without hematologic recovery	3 (3.5)	12 (14%)
Platelets ($x10^3/mm^3$), median (range)	146.0 (127.0–173.0)	153.0 (104.0–287.0)
Hemoglobin (g/dL), median (range)	12.7 (12.5–14.0)	12.9 (11.3–15.4)
ANC post treatment ($x10^3/mm^3$)		
Patients with post treatment ANC	12 (14.0)	20 (14.1)
Mean (SD)	1.7 (0.86)	2.2 (1.60)
range	0.5–3.1	0.1–5.5
Infection[c]		
Infective event rate		
Mean (SD)	0.66 (0.55)	0.77 (0.86)
Median	0.40	0.50
Infection rate (infections/cycle)		
Mean (SD)	0.16 (0.31)	0.25 (0.58)
range	0–15	0–3.0
P-value	0.45	
	n (%)	n (%)
Patients with infections	27 (31)	31 (36)
Patients with infective events[d]	33 (38)	38 (45)
Total number of infective events	80	131
Patients hospitalized	30 (35)	37 (44)
Total number of hospitalizations	43	54
Overall		
Mean (SD)	0.50 (0.78)	0.64 (0.86)
Range	0–3	0–3
P-value	0.26	
Hospitalizations per cycle		
Overall		
Mean (SD)	0.17 (0.42)	0.15 (0.29)
Range	0–3	0–2
P-value	0.49	

Table 2 (continued)

	FCR	PCR
Total number hospitalization days		
Overall		
Mean (SD)	3.15 (6.37)	4.75 (8.61)
Range	0–35	0–52
P-value	0.19	
Hospitalization days per cycle		
Overall		
Mean (SD)	1.30 (3.64)	1.17 (2.71)
Range	0–20	0–17
P-value	0.25	
Reason for Rx Discontinuation		
Completed protocol	47 (51%)	46 (50%)
Toxicity	29 (32%)	26 (28%)
Other	8 (9%)	8 (9%)
Patient request/withdrew consent	6 (7%)	4 (4%)
Investigator request	1 (1%)	3 (3%)
Failed entry	1 (1%)	3 (3%)
Progressive disease	0	1 (1%)
Death (sepsis)	0	1 (1%)
Total patients surviving[e]	75 (82%)	66 (72%)

[a] Reason for nonevaluability: no efficacy assessment after baseline

[b] hematologic recovery was assessed 2 months post-treatment

[c] infection=febrile events requiring treatment

[d] infective events=temperature >101 without symptoms or temp <101 with symptoms

[e] Causes of death (n FCR/n PCR): cardiopulmonary arrest (1/0), cardiovascular accident (0/2), coronary artery disease (1/0), PD (4/9), GI bleed (1/0), leiomyomauterine increase (0/1), lung cancer (1/0), melanoma (1/0), pneumonia (3/0), renal failure (0/2), respiratory failure (1/2), sepsis (1/3), unknown—no autopsy performed (3/7), progressive disease (4/9)

above analyses of patients >70 years of age revealed significant differences between treatment arms.

An analysis of response, time to response, duration of response, and survival (overall and progression-free) for pretreated vs treatment-naïve patients revealed similar results between FCR and PCR patients. Previously untreated patients had higher response rates, including more CRs and PRs and shortened time to response; treatment naïve PCR patient responded in a median of 2.9 months compared to 3.9 months for previously treated patients in that same treatment arm. Median duration of response had not been reached in either treatment group; however, nearly 20% more treatment naïve FCR patients maintained a response at 24-months compared to the previously treated, FCR patients (85% vs 67%).

Drug Delivery

Drug exposure and dose modification details are summarized in Table 3. Dose delays and reductions were more frequent with FCR.

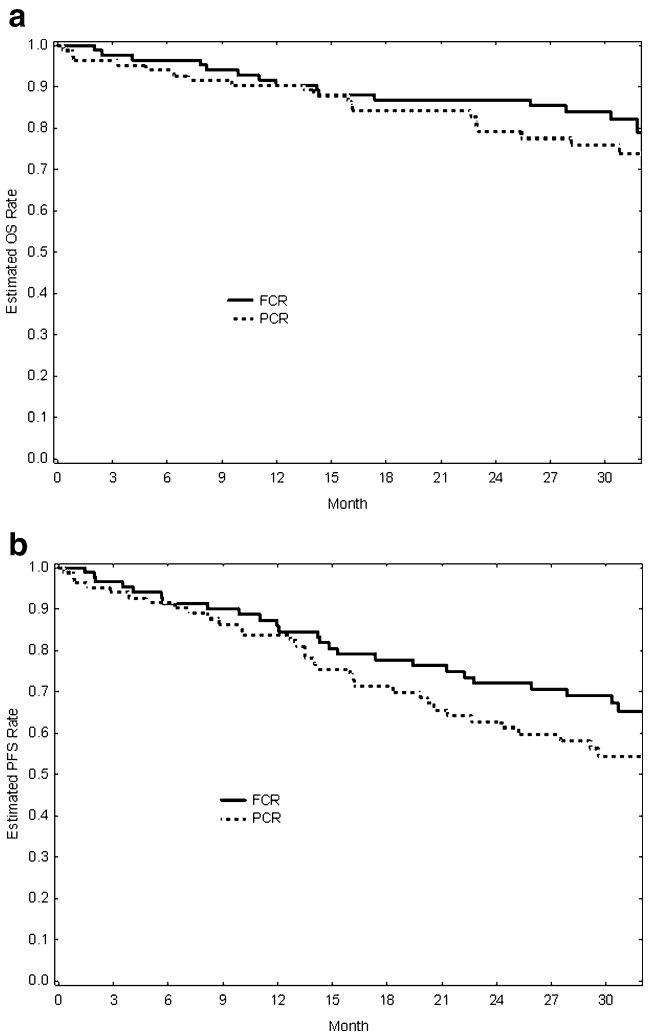

Fig. 1 **a** Overall survival. **b** Progression-free survival

Table 3 Summary of drug delivery and cumulative dose

	FCR	PCR
Total number enrolled	92	92
Total number treated	88	89
Number of cycles	median [range]	median [range]
Cyclophosphamide	6.0 [1–6]	7.0 [1–8]
Fludarabine	6.0 [1–6]	NA
Pentostatin	NA	7.0 [1–8]
Rituximab	6.0 [1–6]	7.0 [1–8]
Cumulative dose		
Cyclophosphamide (g)	5.73 [0.78–9.50]	7.00 [1.20–14.4]
Fludarabine (g)	0.93 [0.13–1.50]	NA
Pentostatin (mg)	NA	48.0 [7.4–96.0]
Rituximab (g)	3.89 [0.49–5.94]	5.19 [0.80–9.03]
Median dose		
Cyclophosphamide (g)	1.15 [0.51–1.58]	1.20 [0.53–1.80]
Fludarabine (g)	0.19 [0.085–0.25]	NA
Pentostatin (mg)	NA	8.0 [3.5–12.0]
Rituximab (g)	0.74 [0.49–0.99]	0.77 [0.59–1.13]
Dose intensity (%)		
Cyclophosphamide	88.0 [50.4–96.5]	87.3 [43.3–97.6]
Fludarabine	85.1 [50.4–97.1]	NA
Pentostatin	NA	87.4 [43.3–99.5]
Rituximab	96.4 [61.3–101.5]	97.2 [65.3–106.7]
Dose modification	n (%)	n (%)
Any delay	31 (35)	24 (27)
Any reduction	31 (35)	26 (29)
Any delay or reduction	46 (52)	37 (42)

NA not applicable

Toxicity

FCR patients tended to have an increased frequency of hematologic toxicity compared to the PCR group. Grade 1–4 adverse events related to infection were similar between the 2 treatment groups as were febrile neutropenia and sepsis. All Grade 3–4 toxicities reported by at least 2 patients in either treatment arm and all infection-related events are summarized in Table 4.

Discussion

This study demonstrates that both FCR and PCR are highly active regimens for CLL patients and can safely be administered in the community setting. The statistical power of the trial was impacted by the decision of the sponsor to close the study prior to completion of planned accrual. This study failed to show that patients treated with PCR had fewer infectious episodes than those treated with FCR. No statistically significant differences were seen in any of the infection related endpoints, including febrile neutropenic events, hospitalization time, or febrile events (Table 2). Statistically nonsignificant trends in most infection-related endpoints favored the FCR arm over PCR, and nonsignificant trends favored PCR in terms of time to hematologic recovery.

Table 2 also summarizes the efficacy of FCR vs PCR. There were no statistically significant differences in efficacy, and most trends favored FCR over PCR. There may be a molecular subgroup of patients that would preferentially benefit from one of the 2 regimens, but in this trial, prognostic factors such as cytogenetic abnormalities/FISH were not required for entry nor collected and such analysis is not available.

The dose of FCR used in this trial differs from the dose of FCR developed by Keating et al and now widely used.

Table 4 Treatment-related adverse events ≥Grade 3 in ≥2 patients

	FCR *N*=88			PCR *N*=89		
	Grade 3 n	Grade 4 n	Total n (%)	Grade 3 n	Grade 4 n	Total n (%)
Hematologic toxicity						
Anemia	6	0	6 (6.8)	3	1	4 (4.5)
Leukocytosis	1	1	2 (2.3)	0	0	0
Leukopenia	14	16	30 (34.1)	12	3	15 (16.9)
Neutropenia	23	38	61 (69.3)	18	33	51 (57.3)
Thrombocytopenia	8	3	11 (12.5)	4	1	5 (5.6)
Nonhematologic toxicity						
Allergic reaction	1	0	1 (1.1)	4	0	4 (4.5)
Asthenia	3	0	3 (3.4)	5	0	5 (5.6)
Confusion	0	0	0	2	0	2 (2.2)
Dehydration	0	0	0	5	0	5 (5.6)
Dyspnea	0	0	0	4	2	6 (6.7)
Febrile neutropenia	7	0	7 (8.0)	5	0	5 (5.6)
Fever	1	1	2 (2.3)	5	0	5 (5.6)
Immunoglobin decreased	2	0	2 (2.3)	0	0	0
Infection	1	0	1 (1.1)	3	0	3 (3.4)
Kidney failure	0	0	0	2	1	3 (3.4)
Myasthenia	0	0	0	2	0	2 (2.2)
Nausea	0	0	0	2	0	2 (2.2)
Pain	1	0	1 (1.1)	4	1	5 (5.6)
Pneumonia	3	0	3 (3.4)	1	0	1 (1.1)
Rash	1	0	1 (1.1)	2	0	2 (2.2)
Sepsis	1	0	1 (1.1)	1	1	2 (2.2)
Vomiting	1	0	1 (1.1)	2	0	2 (2.2)
Infections	Gr 1-2	Gr 3-4	Total (%)	Gr 1-2	Gr 3-4	Total (%)
Chills	17	1	18 (20.4)	16	0	16 (18.0)
Febrile neutropenia	0	7	7 (8.0)	0	5	5 (5.6)
Fever	20	2	22 (25.0)	26	5	31 (34.8)
Infection	5	1	6 (6.8)	3	3	6 (6.7)
Urinary tract infection	3	1	4 (4.5)	2	0	2 (2.2)
Neutropenia	13	61	74 (84.1)	18	51	69 (77.5)
Pneumonia	0	3	3 (3.4)	3	1	4 (4.5)
Sepsis	0	1	1 (1.1)	0	2	2 (2.2)

Grade 1 alopecia occurred in 3 FCR and 6 PCR patients; Grade 2 alopecia was limited to 1 FCR patient

At the time the current trial was developed, it was unclear which FCR regimen would be used most commonly. There has been no direct comparison of these 2 different FCR regimens, so it is difficult to assess whether this had any impact on the results of this trial. PCR dosing is similarly not standardized. In this trial the PCR dose initially developed by Weiss and colleagues [12] was utilized. Subsequently Kay et al [13] published results of a different dosing regimen. The Kay regimen differs in dosing only in the dose of pentostatin, using 2 mg/m^2 each cycle rather than the 4 mg/m^2 used by Weiss and in the current trial. The current trial suggests PCR is less efficacious than FCR; however, it is hard to imagine that a lower dose of pentostatin would improve the efficacy of PCR, though again no direct comparisons of these 2 regimens have been completed.

Since there was published information to suggest that PCR might be particularly effective in patients over the age of 70 [13, 14], an unplanned, retrospective subgroup analysis of patients over the age of 70 was conducted in this trial. Those results are summarized previously in this paper (see Treatment Outcomes). Although the numbers in our subset analyses were small and did not permit statistical comparison, there was nothing to suggest that the outcomes were any different in older patients than the overall patient groups, nor was there evidence of a major advantage of

either regimen in older patients either for safety or efficacy. An unplanned analysis by prior treatment, or treatment naïve, gave similar results. Response and survival data tended to favor previously untreated FCR patients.

Complete and overall response rates reported in this trial (Table 2) are considerably lower than those previously reported for either regimen from single institutions. There are several likely contributing factors to this observation. This was a large multicenter community-based trial, with a different patient mix than that seen at university referral centers. The response definitions utilized in the current trial were extremely rigorous and were applied very conservatively. Some patients did not receive end of therapy bone marrow examinations required to be considered a CR. It is the opinion of the authors that the responses reported in this trial probably under represent the clinical activity of either regimen.

Conclusion

Chemoimmunotherapy should be considered the standard of care for the treatment of CLL. It can be safely administered in the community setting with efficacy seen in patients both over and under the age of 70. There is no compelling reason to favor PCR over FCR in the treatment of CLL, and FCR should be considered the standard backbone going forward in the treatment of CLL.

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Manufacturer name Pentostatin (Nipent ®, Hospira, Inc. [formerly SuperGen, Inc.])
Cyclophosphomide—generic preparations are available and were used at the discretion of the treating physician.
Rituximab (Rituan ®, Genentech/biogen idec)
Fludarabine—generic preparations are available and were used at the discretion of the treating physician.

Appendix

The following medical oncologists from the US Oncology Research network also participated in this study: Robert J. Belt, Shawnee Mission, KS; Paul D. Richards, Salem, VA; Peter J. Schlegel, Spokane, WA; Raymond Taetle, Tucson, AZ; Patrick V. Acevedo, Ocala, FL; Robert L. Anderson, Waco, TX; Arvind Bhandari, Sugar Land, TX; Ernest W. Cochran Jr., Paris, TX; Philip Y. Dien, Burnsville, MN; David C. Faragher, Aurora, CO; Maria Regina Carrillo Flores, Winter Park/Orlando, FL; Yousuf A. Gaffar, Westminster, MD; Matthew T. Gall, Burnsville, MN; Edward R. George, Norfolk, VA; Timothy K. George, Odessa, TX; Robert H. Gersh, Spokane, WA; Houston E. Holmes, III, Dallas, TX; Pankaj Khandelwal, Odessa, TX; Kathryn S. Kolibaba, Vancouver, WA; Peter X. Lamparello, Latham, NY; Deborah L. Lindquist, Sedona, AZ; Robert L. Marsh, Fairfax, VA; Joseph J. Muscato, Columbia, MO; Rajesh Nahar, Kingston, PA; Sucharu Prakash, Paris, TX; Robert N. Raju, Dayton/Kettering, OH; Michael S. Roberts, Scottsdale, AZ; Steven R. Rousey, Edina, MN; Robert L. Ruxer Jr., Fort Worth, TX; Michael A. Savin, Dallas, TX; Russell C. Tolley, Thornton, CO; Frank T. Ward, Tyler, TX; Ira L. Zackon, Latham, NY; Rony Abou Jawde, St. Joseph, MO; Radhika C. Acharya-Leon, Littleton, CO; Jose M. Acostamadiedo, Elizabeth City, NC; Carlos A. Alemany, Ocoee, FL; Stephen P. Anthony, Spokane, WA; David N. Barrera, Fort Worth, TX; Rebecca E Barrington, Kerrville, TX; Stephen B. Beck, Birmingham, AL; Sridhar Beeram, San Antonio, TX; Maury B. Berger, Ocala, FL; William R. Berry, Raleigh, NC; Anil K.V. Bhogaraju, Lewisville, TX; Michael A. Boxer, Tucson, AZ; Thomas E. Boyd, Yakima, WA; Barry D. Brooks, Dallas, TX; Donald J. Brooks, Minneapolis, MN; Elizabeth E. Campbell, Raleigh, NC; Karen M. Carr, Midland, TX; Ashis K. Chakrabarti, Terre Haute, IN; Benjamin L. Cho, Eugene, OR; Jolanta U. Cichon, Denton, TX; Paul R. Conkling, Norfolk, VA; Linda S. Couch, Longview, TX; Jay G. Courtright, Dallas, TX; John M. Davis II, Lee's Summit, MO; Yuhoe Gia Dice, San Antonio, TX; Harry G. Dunn, Latham, NY; Charles F. Eisenbeis, Cary, NC; Maha A. Elkordy, Cary, NC; James B. Ellis, San Antonio, TX; William A. Fintel, Salem, VA; Thomas P. Flynn, Minneapolis, MN; Elke K. Friedman, Norfolk, VA; Sandeep S. Gill, Bedford, TX; William L. Gluck, Greenville, SC; Allen Greenberg, Plantation, FL; Manish Gupta, Garland, TX; Elizabeth A Harden, Newport News, VA; James W. Hathorn, Durham, NC; Lanny I. Hecker, Phoenix, AZ; John D. Hunter, Seneca, SC; Sharad K Jain, Denton, TX; John F. Kessler, Newport News, VA; Steven J. Ketchel, Tucson, AZ; Darren M. Kocs, Austin, TX; Peter A. Kovach, Eugene, OR; Flavio Kruter, Owings Mills, MD; Aparna R. Kumar, Tyler, TX; Douglas J. Lee, Seattle, WA; Gary L. Lee, (deceased) Eugene, OR; Jae H. Lee, Eugene, OR; Lixin Liao, Arlington, TX; Keith W. Logie, Fishers, IN; Regan M. Look, Portland, OR; Jose A. Lopez, Fredericksburg, TX; Jeffrey V. Matous, Denver, CO; Kristi J. McIntyre, Dallas, TX; Scott A. McKenney, Beaumont, TX; Richard J. McKittrick, Kansas City, MO;

Anton M. Melnyk Jr., Abilene, TX; Mathew Miceli, Ocala, FL; Mohammed K. Nashawaty, Edina, MN; Jairo R. Olivares, Garland, TX; Alvin L. Otsuka, Thornton, CO; Mrugesh P. Patel, Bedford, TX; Kelly B Pendergrass, Kansas City, MO; James B Puckett, Asheville, NC; Syed N. Raza, Abilene, TX; Randy S. Rich, Arlington Hts., IL; Robert M. Rifkin, Denver, CO; Bruce H. Saidman, Kingston, PA; Robert L. Sayre, Colorado Springs, CO; Mark D. Sborov, Edina, MN; John F. Schwerkoske, St. Paul, MN; John E. Seng, Minneapolis, MN; John M. Shaw, Chicago, IL; Mark Sienko, Spokane, WA; Paramjeet Singh, Cary, NC; Mark A. Sitarik, Boulder, CO; David A. Smith, Vancouver, WA; Gary Spitzer, Greenville, SC; Valiant D. Tan, Elizabeth City, NC; Dina J. Tebcherany, Austin, TX; Stephen J. Tremont, Raleigh, NC; Michael C. Trendle, Columbia, MO; Kent A. Tucker, Birmingham, AL; Jeffery C. Ward, Edmonds, WA; Robert S. Wehbie, Raleigh, NC; Eric L. Weinshel, Edina, MN; Charles S. White, III, Dallas, TX; Gary M. Wright, Ocala, FL; Hillary H. Wu, Fishers, IN.

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