Treatment of Relapsed Chronic Lymphocytic Leukemia by 72-Hour Continuous Infusion or 1-Hour Bolus Infusion of Flavopiridol: Results from Cancer and Leukemia Group B Study 19805

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Abstract

Purpose: Flavopiridol has *in vitro* activity in chronic lymphocytic leukemia (CLL) and promotes apoptosis independent of p53 function or prior fludarabine exposure. We sought to determine if flavopiridol has activity in previously treated CLL using two schedules of administration.

Patients and Methods: Patients with previously treated CLL were enrolled in two sequentially done phase II studies. Patients in the first trial received flavopiridol (50 mg/m^2/d) as a continuous infusion (CI) for 72 hours every 2 weeks. Patients in the second trial received flavopiridol 50 mg/m^2 as a 1-hour bolus (IVB) daily for 3 days repeated every 3 weeks. Patients received up to 12 (CI cohort) or 8 (IVB cohort) cycles of therapy.

Results: Fifteen patients were enrolled in the 72-hour CI phase II trial; 6 (40%) had intermediate-risk (Rai stage I or II) and 9 (60%) had high-risk (Rai stage III and IV) stages. No responses were noted in this group; 27% had stable disease and 73% had progressive disease. Thirty-six patients were enrolled in the second IVB trial, with 13 (36%) having intermediate and 23 (64%) having high-risk disease. Four patients (11%) had partial responses, 19 (53%) had stable disease, and 13 (36%) had progressive disease. The progression-free survival for responders in the IVB trial was 3, 3, 9, and 19 months. The median progression-free survival was 2 months [95% confidence interval (95% CI), 1.8-3.8] for patients in the CI trial and 3 months (95% CI, 2.5-7.4) for the IVB trial. The median overall survival was 27 months (95% CI, 20-42) for the CI trial and 24 months (95% CI, 18-31) for the IVB trial. Toxicity was manageable and included mainly myelosuppression, infections, diarrhea, and fatigue.

Conclusions: Flavopiridol has modest, schedule-dependent clinical activity in relapsed CLL and warrants future investigation utilizing alternative schedules of administration.

Chronic lymphocytic leukemia (CLL) is one of the most common types of adult leukemia but is incurable with current therapies including fludarabine, rituximab, and alemtuzumab. Developing new therapies for patients with CLL, particularly those with fludarabine-refractory disease or p53 mutations and/or deletions, remains a high priority.

The broad cyclin-dependent kinase inhibitor flavopiridol (National Service Center 649890) may be one such therapy. Studies from several laboratories noted that flavopiridol effectively induces apoptosis in both CLL cell lines and human CLL cells *in vitro* at concentrations attainable in the clinic (1–3). Additionally, flavopiridol seems to be a p53-independent agent and down-modulates select antiapoptosis genes including *mcl-1* and *XIAP* (1–3). These preclinical studies provide justification for pursuing clinical studies of flavopiridol in CLL.

A variety of different schedules of administration have been explored with flavopiridol including 72-hour continuous infusion (CI; refs. 4, 5), 24-hour CI (6), and a 1-hour bolus (IVB; ref. 7). The 1-hour IVB schedule recommended for phase II studies was 50 mg/m^2 administered on days 1, 2, and 3 (7). The trials all have generally short duration neutropenia, diarrhea, cytokine release syndrome (8), and fatigue. No significant clinical activity has been observed using 72-hour infusion flavopiridol as a single agent for solid tumors and mantle cell lymphoma (9–13). Modest activity in mantle cell lymphoma (12% partial response rate; ref. 14) has been noted with the 1-hour 50 mg/m^2 $\times$ 3 days schedule. Herein, results

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of a Cancer and Leukemia Group B trial that pursued two sequential studies examining the efficacy of single agent flavopiridol utilizing the 72-hour CI and 1-hour IVB schedules in CLL are described.

Materials and Methods

Subjects. Patients were enrolled in this multicenter trial done by the Cancer and Leukemia Group B after approval by local institutional review boards. All patients gave written informed consent. Patients were required to have histologically documented CLL as defined by the modified National Cancer Institute (NCI) guidelines (15) and to require therapy according to these same criteria. Patients with stage I and II disease had symptomatic lymphadenopathy. Patients had all received at least one prior chemotherapy regimen but not greater than three regimens. Patients may have received one prior nonradiolabeled antibody treatment (e.g., Campath-1H or rituximab) in addition to the maximum limit of three chemotherapy treatments. Required clinical features included age older than 17 years, symptomatic by the NCI 96 criteria (15), and not pregnant. The serum creatinine and total bilirubin levels were required to be less than or equal to 1.5 times the normal value.

Pretreatment evaluation. All patients underwent pretreatment screening that included history, physical examination, laboratory, and X-ray studies before entry into the trial. These tests included a complete blood count with differential, electrolytes, blood urea nitrogen, creatinine, total protein, albumin, calcium, phosphate, lactate dehydrogenase, uric acid, total bilirubin, alanine aminotransferase, aspartate aminotransferase, immunoglobulins, direct antiglobulin test, chest X-ray, and bone marrow aspirate and biopsy.

Treatment and dose modifications. All patients received allopurinol 300 mg/d beginning 1 day before initiation of treatment and continued during the first 2 weeks of therapy. The first trial (n = 15 patients) administered flavopiridol (50 mg/m^2) daily for 3 consecutive days by continuous infusion every 2 weeks. Patients could discontinue therapy for stable disease without improvement after four treatments. Otherwise, patients continued therapy in the absence of progression or toxicity that prohibited further treatment for a maximum of 12 treatments of flavopiridol. The second trial (n = 36 patients) given flavopiridol (50 mg/m^2) as a 1-hour IVB daily for 3 consecutive days repeated every 3 weeks. Patients could discontinue therapy for stable disease without improvement after two treatments. Otherwise, patients continued therapy in the absence of progression or toxicity that prohibited further treatment for a maximum of eight treatments of flavopiridol.

If treatment was tolerated with grade 2 or less diarrhea or fatigue that resolves within 5 days and no other grade 3 toxicity, then the dose of flavopiridol remained constant. If grade 3 or 4 diarrhea developed, then diarrhea treatment with cholestipol (5 grams orally every 6 hours) and loperamide (4 mg every 4 hours while awake) was initiated immediately and prophylaxis was administered with subsequent treatments. For grade 3 diarrhea, the dose was not reduced unless this recurred despite prophylaxis. Patients developing grade 4 diarrhea had a 33% dose reduction (i.e., to 2 days of therapy), but were reescalated to full dose on subsequent cycles if severe diarrhea did not recur. Patients experiencing fatigue were not re-treated until this symptom has resolved to grade 2 or less. Patients experiencing grade 3 or 4 fatigue for greater than 5 days had a 33% dose reduction. If recurrent grade 3 or fatigue persisted at this lower dose, a second dose reduction occurred and patients received 1 day of therapy (50 mg/m^2 for 1 day; total dose, 50 mg/m^2). If recurrent fatigue persisted at this dose, the patient was removed from protocol therapy. Grade 3 or 4 hematologic toxicity mandated a 33% dose reduction. For renal, pulmonary, hepatic, and other toxicities of grade 3 and greater related to flavopiridol, therapy was discontinued.

Assessment of toxicity and response. Hematologic toxicity was graded according to the modified NCI criteria for CLL (15) and nonhematologic toxicity was graded according to the NCI Common Toxicity Criteria. Patients were assessed for disease response with a detailed clinical evaluation (physical exam with lymph node, liver, and spleen measurement) and complete blood count with differential after four and eight treatments in the CI schedule and after three and six cycles of therapy in the IVB schedule. Criteria for response used the Revised NCI-sponsored Working Group Guidelines (15). As specified by these guidelines, a response had to be maintained for a period of 2 months. Response duration was defined in responders from the time the response was first noted until progression or last follow-up. Progression-free survival was defined similarly, except that follow-up began for all patients from the time of initiation of treatment. Progression was defined using the NCI 96 criteria (15). Survival time was measured from the time of initial treatment until the time last seen alive (censored) or death (event). Survival probabilities for progression free survival and overall survival were estimated using the method of Kaplan-Meier (16). The SEs for these estimates were obtained using the variance estimate as previously described (17).

Results

Patient characteristics. Fifteen patients, nine of whom were fludarabine-refractory, were enrolled and treated in the 72-hour CI trial between March 01, 1999 and October 11, 2000, after which time further enrollment was discontinued due to lack of efficacy. Thirty-six patients, 18 of whom were fludarabine refractory, were then enrolled and treated in the 1-hour IVB schedule of flavopiridol between November 27, 2000 and June 18, 2002. The pretreatment features of the patients enrolled in the two studies are summarized in Table 1.

Response to treatment and treatment outcome. All patients were evaluable for response and toxicity assessments. Among the 15 patients enrolled in the 72-hour CI trial, there were no complete or partial responses. Four patients (27%) had stable disease and 11 (63%) had progressive disease. No patients completed all 12 courses of therapy with a median of 3.5 treatments taken (range 1-10). No evidence of acute tumor lysis was observed. The median progression-free survival for the entire group was 2 months (95% confidence interval, 2-4), as depicted in Fig. 1. Thirteen patients have died; the median survival is 27 months (95% confidence interval, 20-42), as depicted in Fig. 2.

Among the 36 patients enrolled in the 1-hour IVB trial, there were no complete response; 4 (11%) showed partial response, 19 (53%) had stable disease, and 13 (36%) had progressive disease. All four patients who responded had fludarabine refractory CLL. Seven patients completed all eight planned courses of therapy (median, 3; range, 1-8). One patient had evidence of tumor lysis syndrome with an increase in potassium to 5.8 mmol/L and phosphate to 5.3 mg/dL accompanied by a drop in WBC from 267 $\times$ 10^9/L to 62 $\times$ 10^9/L baseline to day 3 of therapy. This patient had concomitant grade 3 diarrhea, was managed medically with hydration and urine alkalination, and did not require dialysis. This patient attained a partial response that was maintained for 3 months. The time to progression for each of the four responders was 3, 3, 9, and 19 months. The median progression-free survival for the entire group was 3 months (95% confidence interval, 3-7) as depicted in Fig. 1. Twenty-three (64%) of the patients have died after a median survival of 24 months (95% confidence interval, 18-31) as depicted in Fig. 2.

Toxicity. The toxicities observed in each of the two trials are summarized in Table 2. Overall, patients experienced one or more grade 3 and 4 toxicities; 20% and 27% for the CI trial and

Table 1. Pretreatment characteristics of patients enrolled in CI and IVB studies

	72-hour CI trial, *N* = 15	1-hour IVP trial, *N* = 36
Median age (range)	63 (47-80)	61 (37-81)
Stage		
Rai intermediate risk	40%	36%
Rai high risk	60%	64%
% Female	27%	33%
Performance status		
0	53%	34%
1	47%	60%
2	0%	6%
Median number of prior therapies (range)	2 (1-3)	2 (1-5)
% Fludarabine refractory	60%	50%
Median (range) leukocyte count ($\times 10^9$/L)	15.7 (1-33.1)	16.4 (0.7-96.6)
Median (range) hemoglobin count (g/dL)	11.3 (7.9-17.4)	11.1 (5.9-16.0)
Median (range) platelet count ($\times 10^9$/L)	80 (9-209)	85 (11-339)
% with splenomegaly	67%	47%
% with hepatomegaly	29%	18%
% with adenopathy	80%	86%

39% and 33% for the IVB trial. Common grade 3 and 4 toxicities in both studies included granulocytopenia, anemia, infection, diarrhea, and fatigue. There were no grade 5 toxicities in the CI trial. The fatal myocardial infarction found in one patient in the IVB trial was not treatment related as the patient developed progressive disease on day 17 of cycle 5 with a rapidly enlarging spleen. He was admitted for small bowel obstruction and subsequently suffered a fatal myocardial infarction.

Discussion

In this study, we have observed that the cyclin-dependent kinase inhibitor flavopiridol, when administered as a 72-hour CI every 2 weeks, has no clinical activity in previously treated CLL. In contrast, flavopiridol by IVB daily for 3 consecutive days every 3 weeks showed modest activity, with 4 patients (11%) attaining a partial response, 19 (53%) having stable disease, and only 13 (36%) having progressive disease as their best response. Although the four responding patients had fludarabine-refractory disease, the overall survival of the entire group of patients is longer than the large alemtuzumab phase II trial (18), likely reflective of a less heavily treated population. Unfortunately, this study did not include genetic studies for interphase cytogenetics, p53 mutational status, V_H mutational status, or ZAP-70 expression. Future investigation of flavopiridol should include these. With both schedules of administration, toxicity was modest, mainly consisting of reversible myelosuppression, diarrhea, infection, and fatigue. Overall, these studies suggest that flavopiridol in CLL is highly schedule dependent with predictable toxicity with clinical

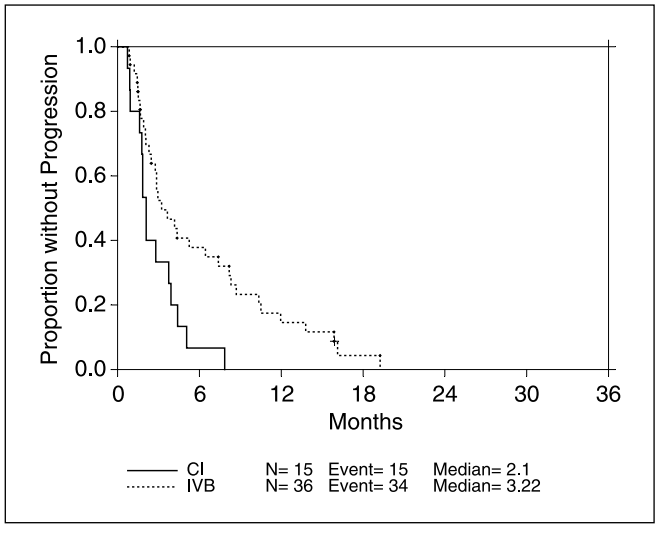

Fig. 1. Progression-free survival for all patients with previously treated CLL treated with flavopiridol by 72-hour CI (*black line*, $n = 15$) and 1-hour IVB daily for 3 consecutive days (*dotted line*, $n = 36$) in Cancer and Leukemia Group B 19805.

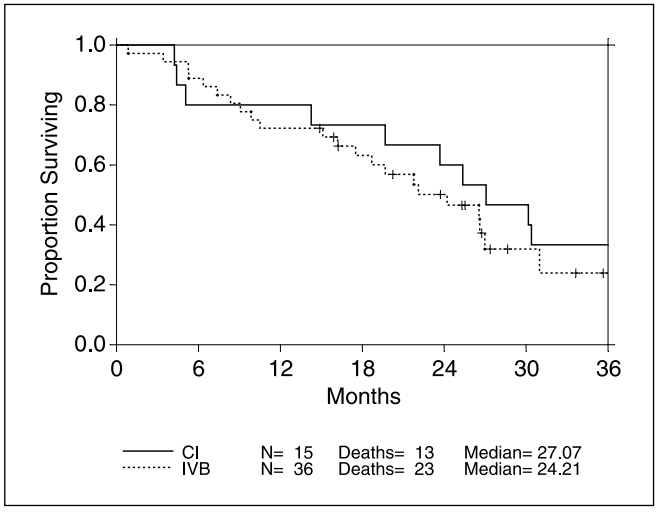

Fig. 2. Overall survival for all patients with previously treated CLL treated with flavopiridol by 72-hour CI (*black line*, $n = 15$) and 1-hour IVB daily for 3 consecutive days (*dotted line*, $n = 36$) in Cancer and Leukemia Group B 19805.

Table 2. Number (%) of patients with toxicity during treatment

Toxicity	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Neutropenia				
CI	1 (7)	1 (7)	1 (7)	4 (27)
IVB	4 (11)	2 (6)	9 (25)	9 (25)
Thrombocytopenia				
CI	4 (27)	1 (7)	3 (20)	1 (7)
IVB	6 (17)	9 (25)	6 (17)	2 (6)
Anemia				
CI	0 (0)	0 (0)	0 (0)	0 (0)
IVB	10 (28)	10 (28)	2 (6)	1 (3)
Infection				
CI	1 (7)	2 (13)	3 (20)	0 (0)
IVB	0 (0)	3 (8)	7 (19)	2 (6)
Diarrhea				
CI	2 (13)	2 (13)	1 (7)	0 (0)
IVB	10 (28)	11 (31)	13 (36)	0 (0)
Cough				
CI	0 (0)	0 (0)	0 (0)	0 (0)
IVB	0 (0)	0 (0)	1 (3)	0 (0)
Dyspnea				
CI	0 (0)	1 (7)	0 (0)	0 (0)
IVB	0 (0)	2 (6)	1 (3)	0 (0)
Fatigue				
CI	4 (27)	2 (13)	0 (0)	0 (0)
IVB	17 (47)	8 (22)	4 (11)	0 (0)
Weight loss				
CI	1 (7)	0 (0)	1 (7)	0 (0)
IVB	0 (0)	0 (0)	0 (0)	0 (0)
Pain				
CI	3 (20)	1 (7)	0 (0)	0 (0)
IVB	4 (11)	3 (8)	0 (0)	0 (0)
	4 (27)	1 (7)	0 (0)	0 (0)
	2 (6)	1 (3)	0 (0)	0 (0)
Maximum toxicity (per patient)				
CI	1 (7)	6 (40)	3 (20)	4 (27)
IVB	2 (6)	6 (17)	14 (39)	12 (33)

activity. Indeed, the efficacy observed in the 72-hour CI (13) and 1-hour IVB (14) studies of mantle cell lymphoma mimics that observed in CLL. Further schedule optimization might therefore lead to improved efficacy of single agent flavopiridol in lymphoid diseases.

Despite the remarkable activity of flavopiridol *in vitro* with both short and long exposures, one must ask why more clinical activity was not observed in this trial. Indeed, pharmacokinetic data from the 72-hour phase I and II CI studies done by others attained plasma drug concentrations (200-400 nmol/L) that induced apoptosis *in vitro* (4, 5, 12, 19). Although no pharmacokinetic studies were done in this trial, studies done to date have shown relatively consistent pharmacokinetics across different patient populations (4, 5, 12, 19). One explanation for poor concordance between the promising *in vitro* results and disappointing clinical results may be due to increased flavopiridol drug binding to human plasma proteins as compared with protein in the FCS typically used for *in vitro* studies with this agent. Based on poor results in the 72-hour and 24-hour trials done by Aventis Pharmaceuticals in fludarabine-refractory CLL (20)[7] our group investigated the possibility that differential protein binding could exist between these two culture media. These studies showed that substitution of human plasma for FCS *in vitro* resulted in a decrease in free drug level from 63-100% to 5-8%, with an increase in 1-hour and 24-hour LC_{50} values from 670 and 120 nmol/L to 3,510 and 470 nmol/L, respectively (21). This increase in the *in vitro* LC_{50} may be critical, as the 24-hour LC_{50} of 470 nmol/L has not been achieved *in vivo* with the 72-hour CI schedule (12, 22). Additionally, the 1-hour LC_{50} concentration for CLL cells in human serum was not obtained in the solid tumor phase I trial exploring this schedule (7). Thus, the CI or IVB dosing schedule may not achieve pharmacologically effective drug concentrations of flavopiridol, thereby explaining the absence of activity in the CI schedule and the marginal activity with the IVB schedule described herein.

[7] Jose Ramon-Suarez, personal communication.

Where does the development of flavopiridol in CLL go from here? Given the novel mechanism of action of this agent and the ability of flavopiridol to induce apoptosis independent of p53 dysfunction, this agent remains a worthwhile therapy to develop. One strategy includes combining the 1-hour or 24-hour schedule of administration with other therapeutic agents to generate synergy in previously described tumor systems *in vitro* (23–27). This is currently being pursued by several investigators with fludarabine, rituximab, and other targeted therapies such as the histone deacetylase inhibitor depsipeptide. Another strategy would be to further optimize the schedule of administration of flavopiridol given the schedule dependence observed to date. Based on the pharmacokinetic studies described above related to differential protein binding in FCS and human serum, pharmacokinetic modeling from the Aventis 24-hour CI study suggested that a 30-minute IVB followed by a 4-hour CI schedule could attain a concentration of flavopiridol that induces apoptosis in primary CLL cells. Based on this modeling, an NCI-sponsored clinical study has been initiated in fludarabine refractory CLL. In this study, a 30 mg/m^2 dose is administered as a bolus followed by a second 30 mg/m^2 4-hour dose (total 60 mg/m^2 per week) every week for 4 consecutive weeks followed by a 2-week observation period with 10 mg/m^2 incremental increases in the IVB and 4-hour dose with subsequent cohorts. A preliminary report of this study has included responses and a dose-limiting toxicity of acute tumor lysis syndrome (28). Based on these promising results, other trials in lymphoid malignancies, acute leukemia, and solid tumors are now being pursued utilizing this novel schedule. Alternative schedules of administration or combinations with other drugs may be required to fully exploit the benefits of flavopiridol in lymphoid malignancies.

Appendix 1

The following institutions participated in this study:

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