Phase II Study of Flavopiridol in Relapsed Chronic Lymphocytic Leukemia Demonstrating High Response Rates in Genetically High-Risk Disease

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Submitted February 24, 2009; accepted June 22, 2009; published online ahead of print at www.jco.org on October 13, 2009.

Supported by National Institutes of Health Grants No. U01 CA76576, 2 P01 CA81534, NO1 CM62207, K23 CA102276-05, and P30 CA 16058; the Leukemia and Lymphoma Society; and the D. Warren Brown Foundation.

Presented in part at the 44th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2008, Chicago, IL; the European Hematology Association New Drugs in Hematology Conference, October 5-7, 2008, Bologna, Italy; and the 50th Annual Meeting of the American Society of Hematology, December 6-9, 2008, San Francisco, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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0732-183X/09/2735-6012/\$20.00

DOI: 10.1200/JCO.2009.22.6944

ABSTRACT

Purpose

Patients with chronic lymphocytic leukemia (CLL) with high-risk genomic features achieve poor outcomes with traditional therapies. A phase I study of a pharmacokinetically derived schedule of flavopiridol suggested promising activity in CLL, irrespective of high-risk features. Given the relevance of these findings to treating genetically high-risk CLL, a prospective confirmatory study was initiated.

Patients and Methods

Patients with relapsed CLL were treated with single-agent flavopiridol, with subsequent addition of dexamethasone to suppress cytokine release syndrome (CRS). High-risk genomic features were prospectively assessed for response to therapy.

Results

Sixty-four patients were enrolled. Median age was 60 years, median number of prior therapies was four, and all patients had received prior purine analog therapy. If patients tolerated treatment during week 1, dose escalation occurred during week 2. Dose escalation did not occur in four patients, as a result of severe tumor lysis syndrome; three of these patients required hemodialysis. Thirty-four patients (53%) achieved response, including 30 partial responses (PRs; 47%), three nodular PRs (5%), and one complete response (1.6%). A majority of high-risk patients responded; 12 (57%) of 21 patients with del(17p13.1) and 14 (50%) of 28 patients with del(11q22.3) responded irrespective of lymph node size. Median progression-free survival among responders was 10 to 12 months across all cytogenetic risk groups. Reducing the number of weekly treatments per cycle from four to three and adding prophylactic dexamethasone, which abrogated interleukin-6 release and CRS ($P \leq .01$), resulted in improved tolerability and treatment delivery.

Conclusion

Flavopiridol achieves significant clinical activity in patients with relapsed CLL, including those with high-risk genomic features and bulky lymphadenopathy. Subsequent clinical trials should use the amended treatment schedule developed herein and prophylactic corticosteroids.

J Clin Oncol 27:6012-6018. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world. CLL patients have benefited from therapeutic advances in the last decade, including monoclonal antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52), and combination chemoimmunotherapy regimens.¹⁻⁵ However, such treatments are not curative, and patients invariably experience relapse. Additionally, patients with high-risk genomic features such as del(17p13.1) respond poorly to traditional therapies. Although allogeneic stem-cell

transplantation (SCT) is potentially curative, many high-risk patients are not transplantation candidates because of bulky lymphadenopathy or comorbid illnesses. In addition, although alemtuzumab and high-dose methylprednisolone have activity in select patients with CLL with del(17p13.1), both therapies are associated with significant immunosuppression and infectious complications.⁶⁻¹⁰ Therefore, identification of effective, nonimmunosuppressive, novel treatments against genetically high-risk CLL would represent a major therapeutic advance.

Flavopiridol is a broad cyclin-dependent kinase inhibitor that induces apoptosis of CLL cell lines and

primary human CLL cells in vitro at concentrations that are attainable clinically.¹¹⁻¹⁶ Furthermore, flavopiridol induces apoptosis independently of p53.¹⁷ Despite its biologic activity, initial clinical studies using 24- to 72-hour continuous intravenous infusion (CIVI) schedules failed to demonstrate clinical activity in a variety of malignancies including CLL.¹⁸⁻²⁴ Subsequent studies to elucidate this discordance between the preclinical activity of flavopiridol and these initially disappointing clinical results demonstrated high drug binding to human serum but minimal binding to bovine serum, resulting in underestimation of the drug concentration necessary for clinical efficacy.²⁵ On the basis of this observation, a phase I dose-escalation study of a novel, pharmacokinetically derived dosing schedule administered flavopiridol by 30-minute intravenous bolus (IVB) followed by 4-hour CIVI.^{26,27} This schedule was clinically active, with a dose-limiting toxicity (DLT) of acute tumor lysis syndrome (TLS). Here, we describe a large phase II study of single-agent flavopiridol that confirms our preliminary phase I findings and demonstrates the effectiveness of flavopiridol against genetically high-risk CLL.

PATIENTS AND METHODS

Patients

Patients were enrolled onto this National Cancer Institute (NCI)-sponsored clinical study (NCI 7000, The Ohio State University [OSU] 0491) after approval by the OSU Institutional Review Board. All patients provided written informed consent. Patients had CLL or prolymphocytic leukemia arising from CLL, had received at least one prior chemotherapy regimen, and required treatment according to NCI 1996 criteria.²⁸ Prior SCT was allowed. Patients were age 18 years or older and had Eastern Cooperative Oncology Group performance status of 0 to 2, creatinine less than 2.0 mg/dL, bilirubin less than 1.5 $\times$ the upper limit of normal, transaminases less than 2 $\times$ the upper limit of normal, and WBC count less than 200 $\times$ 10⁹/L. Pregnant women were excluded.

Treatment Plan

Flavopiridol (alvocidib) was administered through a central venous catheter at a dose of 30 mg/m² by 30-minute IVB followed by 30 mg/m² by 4-hour CIVI for dose 1. Patients who did not develop severe TLS underwent dose escalation to 30 mg/m² IVB + 50 mg/m² CIVI for dose 2 and all subsequent treatments. Treatment was administered weekly for four doses every 6 weeks for up to six cycles. Supportive therapy consisted of allopurinol 300 mg daily and valacyclovir 1,000 mg daily (or equivalent) for the duration of treatment. *Pneumocystis carinii* pneumonia (PCP) prophylaxis was administered at the treating physician's discretion, although nearly all patients received sulfamethoxazole/trimethoprim for PCP prophylaxis. Patients received granisetron 2 mg orally for antiemetic prophylaxis.

Amended Treatment Plan

To improve tolerability of the treatment regimen, an NCI- and OSU IRB-approved amendment reduced the cycle length from 42 days to 28 days, reduced the number of treatments per cycle from four (days 1, 8, 15, and 22) to three (days 1, 8, and 15), and administered prophylactic dexamethasone 20 mg IV on each treatment day, prophylactic pegfilgrastim 6 mg on day 16 of each cycle, and ciprofloxacin 500 mg twice daily as prophylaxis as a result of corticosteroids. PCP prophylaxis was unchanged.

Prophylaxis and Management of TLS

As a result of grade 4 to 5 TLS, which was the DLT in the phase I study, patients were closely observed for TLS and were treated as previously described.²⁶ Rasburicase 0.15 mg/kg was administered 2 hours before the first and second doses of flavopiridol, and the ability to perform bedside dialysis was assured. After dose 2, patients were transitioned to outpatient treatment. Patients who required hemodialysis for severe TLS underwent 10

mg/m² reduction of both the IVB and CIVI dose but were allowed to continue therapy.

Assessment of Toxicity and Response

NCI Common Toxicity Criteria of Adverse Events (version 3) and modified NCI Common Toxicity Criteria guidelines for evaluating hematologic toxicity in leukemia were used to grade toxicity. Patients were assessed for clinical response after two, four, and six cycles. The 1996 NCI Working Group response criteria were used.²⁸ Progression-free survival (PFS) was calculated from the date of study entry until time of disease progression or death, whichever came first, censoring patients alive and relapse free at last follow-up. If the best response was not evaluable or stable disease, PFS was measured from the date of study entry until the starting date of subsequent treatment (censored) or the date of death (event). Patients who withdrew from study to undergo an allogeneic SCT were censored at the time of transplantation.

Interphase Cytogenetic and Serial Cytokine Assessment

Pretreatment interphase cytogenetic analysis was performed as previously published.⁷ Assessment of plasma tumor necrosis factor α , interferon gamma, interleukin (IL) -4, IL-6, and IL-10 occurred at 0, 4.5, 8, 12, and 24 hours after treatment initiation using enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN) per manufacturer's directions.

Statistical Considerations

Primary end points were to determine the toxicity and overall response rate (ORR) of flavopiridol. Secondary end points included determination of response in patients with del(17p13.1) and del(11q22.3), PFS, and the association of cytokine release syndrome (CRS) with the increase in specific cytokines. This phase II study used a mini-max Simon two-stage design, with 17 and 15 patients in the two stages, powered at 90% to detect an improvement in ORR from 15% to 35% with $\alpha = .10$. If more than seven of 32 patients responded to therapy, then flavopiridol would be deemed worthy of further study. The protocol was amended to study a modified treatment schedule in 32 additional patients to determine whether tolerability could be improved and to allow improved treatment delivery. Thus, 64 total patients were enrolled.

Associations between treatment cohorts and clinical, demographic, and genomic features were described using the χ^2 or Fisher's exact and Wilcoxon rank sum tests for categorical and continuous variables, respectively. The ORR, with 95% CIs, was determined. The estimated median PFS times were calculated using the Kaplan-Meier method, and the proportional hazards model was used to obtain estimates of hazard ratios for patients with and without genetically high-risk CLL.

Logistic regression was used to test the association between measures of tolerance/toxicity with treatment cohort and to test for the factors most associated with overall response. Variables were treatment cohort; age; sex; number of prior therapies; fludarabine-refractory status; Rai stage; bulky lymphadenopathy; baseline WBC, lactate dehydrogenase, and β_2 -microglobulin levels; and high-risk genomic features. Full descriptions of the logistic regression analysis and the mixed model used to test for the effect of dexamethasone on IL-6 expression can be found in the Appendix (online only).

RESULTS

Patient Characteristics

Sixty-four patients were enrolled. The first 27 patients followed the initial treatment regimen, the next five transitioned to the amended regimen while on study, and the latter 32 followed the amended regimen. Table 1 lists the pretreatment characteristics of all 64 patients and compares characteristics of the pre- and postamendment treatment cohorts. Median age was 60 years (range, 31 to 82 years). Fifty patients (78%) were Rai stage III or IV, and 47 patients (73%) had bulky lymphadenopathy (> 5 cm). Patients had received a median of four prior therapies (range, one to 11 prior therapies). All patients had received prior purine analog therapy (fludarabine,

Table 1. Patient Demographics and Clinical Characteristics, Overall and by Treatment Cohort

Demographic or Clinical Characteristic	All Patients (N = 64)		Preamendment Group (n = 27)		Transition Group (n = 5)		Postamendment Group (n = 32)		P*
	No.	%	No.	%	No.	%	No.	%	
Age, years									
Median	60.5		64		64		57		.007
Range	31-82		41-82		52-70		31-76		
≥ 70	10	16	7	26	1	20	2	6	.07
Female	22	34	9	33	4	80	9	28	.67
Rai stage III/IV	50	78	23	85	5	100	22	69	.22
Bulky lymphadenopathy	47	73	25	93	3	60	19	59	.006
No. of prior therapies									
Median	4		5		6		3		.003
Range	1-11		1-11		2-8		1-8		
Prior purine analog									1.00
Fludarabine	61	95	26	96	4	80	31	97	
Pentostatin only	3	5	1	4	1	20	1	3	
Purine analog refractory	38	59	18	67	3	60	17	53	.29
High-risk genomic feature	47	73	19	70	3	60	25	78	.50
Del(17p13.1)	21	33	8	30	2	40	11	34	.70
Del(11q22.3)	28	44	13	48	2	40	13	41	.56
Complex karyotype†	27	42	13	48	2	40	12	38	.41

*Compares preamendment with postamendment patients, excluding the five transitional patients.

†Defined as three or more cytogenetic aberrations.

n = 61; pentostatin, n = 3). Thirty-eight patients (59%) had purine analog–refractory disease as defined previously.² One patient had experienced treatment failure with prior allogeneic SCT. Twenty-one patients (33%) had del(17p13.1), 28 (44%) had del(11q22.3), and 27 (42%) had a complex karyotype. The two treatment cohorts differed significantly in age ($P = .007$), number of prior therapies ($P = .003$), and presence of bulky lymphadenopathy ($P = .006$). Postamendment patients were younger, had received fewer prior therapies, and had fewer occurrences of bulky lymphadenopathy, thus appearing healthier than preamendment patients.

Toxicity

Toxicities are listed in Table 2 and were similar to toxicities in the phase I study.²⁶ Toxicities were generally transient and related to cytopenias, electrolyte and liver function abnormalities, fatigue, diarrhea, and nonopportunistic infections. Fifty-eight of 62 patients who received at least two flavopiridol doses underwent planned dose escalation. Four patients did not undergo dose escalation (two preamendment and two postamendment) as a result of severe TLS, hyperkalemia, and hyperphosphatemia after dose 1. Three of these four patients required transient hemodialysis but made a full recovery and received additional treatments after 10 mg/m² reduction of both the IVB and CIVI dose. The fourth patient did not require dialysis but did not undergo dose escalation.

Grade 3 to 4 infections requiring IV antibiotics occurred in 25% of patients and were generally related to upper or lower respiratory infections or infections of indwelling central venous catheters. Four patients died of infection during or soon after completion of study treatment, and it was unclear whether flavopiridol contributed to these deaths. An 82-year-old woman died of bilateral pneumonia after one treatment. A 69-year-old woman died of pulmonary strongyloidiasis shortly after completing 3.25 cycles but retrospectively had long-

standing pretreatment eosinophilia. A 48-year-old woman who had experienced treatment failure with allogeneic SCT and had been on chronic corticosteroid therapy and other immunosuppression for graft-versus-host disease died of adult respiratory distress syndrome after developing streptococcal and vancomycin-resistant enterococcal pneumonia and sepsis. Finally, a 58-year-old man with a previous history of breast cancer and non-Hodgkin's lymphoma and with neutropenia as a result of marrow disease at study entry died of *Pseudomonas* and vancomycin-resistant enterococcal sepsis after one cycle. These infections should be evaluated in the context of a highly refractory patient population.

The median number of delivered cycles was four, and 17 patients completed planned therapy. The most common reasons for failure to complete therapy were failure to respond (n = 20), patient choice (n = 10), allogeneic SCT (n = 7), fatigue (n = 4), and fever or infection (n = 4). Several patients who discontinued therapy did so because of their travel distance.

In general, amending the treatment regimen improved tolerability and reduced toxicities. Only one (4%) of 27 preamendment patients completed planned therapy, compared with 15 (47%) of 32 postamendment patients ($P = .003$, adjusted for age, number of prior treatments, and bulky lymphadenopathy). Furthermore, we observed a significant diminishment in CRS symptoms, defined clinically by fever, flushing, tachycardia, and nausea, from 56% to 22% ($P = .01$) and significant decreases in the frequency of TLS ($P = .04$) and nausea/vomiting ($P = .004$) when controlling for age, number of prior treatments, and bulky lymphadenopathy (Table 2). Serial plasma cytokine measurement in the preamendment cohort demonstrated that only IL-6 increased after completion of the 4-hour CIVI. Adjusting for baseline IL-6 expression, the maximum average of IL-6 expression in the preamendment cohort was 25.5 pg/mL at 12 hours (Fig 1). Unlike previous reports, the highest level of IL-6 expression was not related to

Table 2. Common Toxicities in All 64 Patients and by Treatment Cohort

Toxicity	Toxicity Grade (% of patients)		
	All Grades	Grades 1-2	Grades 3-5*
Neutropenia	97	9	88
Preamendment	96	4	93
Postamendment	97	16	81
Anemia	59	53	6
Preamendment	70	63	7
Postamendment	47	41	6
Thrombocytopenia	66	39	27
Preamendment	74	30	44
Postamendment	56	41	16
Infection	67	36	31
Preamendment	63	19	44
Postamendment	66	47	19
Fatigue	94	86	8
Preamendment	89	81	7
Postamendment	97	94	3
Diarrhea	94	30	64
Preamendment	93	41	52
Postamendment	94	22	72
Nausea/vomiting	75	69	6
Preamendment	89	78	11
Postamendment	63	59	3
Anorexia	31	31	0
Preamendment	44	44	0
Postamendment	22	22	0
Anxiety/depression	17	16	2
Preamendment	22	22	0
Postamendment	13	9	3
Tumor lysis syndrome	44	2	42
Preamendment	63	4	59
Postamendment	22	0	22
Cytokine release syndrome	42	34	8
Preamendment	56	41	15
Postamendment	22	19	3
Transaminitis	92	58	34
Preamendment	93	67	26
Postamendment	91	56	34
Hyperbilirubinemia	23	22	2
Preamendment	26	26	0
Postamendment	22	19	3

NOTE. The percentages provided for all 64 patients are equal to the weighted average of the percentages among treatment cohorts.

*The only grade 5 toxicity was infection, occurring in four (6%) of 64 patients.

Fig 1. Prophylactic dexamethasone abolishes increase in plasma interleukin-6 (IL-6) levels induced by flavopiridol. Plasma IL-6 levels were measured in patients treated with flavopiridol who were not (circles) or were (triangles) administered prophylactic dexamethasone.

plete response (CR; 1.6%). Three of the four CR/nPR patients achieved less than 1% CLL in the marrow by flow cytometry. One patient who achieved a CR with 0.3% residual CLL was negative for minimal residual disease (MRD) on subsequent bone marrow biopsy.

Factors normally associated with inferior outcome to standard therapy, such as del(17p13.1), del(11q22.3), elevated β_2 -microglobulin, and bulky lymphadenopathy, did not show a statistically significant association with response (all $P > .50$; Table 3). However, CIs on the difference in response were wide, preventing any strong conclusions about equality in response rate between groups. However, treatment cohort (preamendment and postamendment), WBC, sex, and number of prior therapies were associated with response rate ($P < .20$). These variables were included in a full multivariable model (Table 4). On backward selection, removing number of prior therapies first ($P = .33$), WBC second ($P = .21$), and treatment cohort third ($P = .06$), only sex remained as the most significant variable associated with response ($P = .01$; Table 4). The odds of a woman achieving a response was 4.9 times (95% CI, 1.4 to 17.6 times) the odds of a man achieving a response. Seventeen (77%) of 22 women responded compared with 17 (40%) of 42 men.

PFS

A prospective secondary end point was to assess PFS overall and in patients with high-risk genomic features. Median PFS for all patients was 8.6 months. Of the 34 responders, seven were taken off study

CRS, although patients who developed CRS demonstrated increased IL-6 expression sooner than those who did not develop CRS (data not shown). Prophylactic dexamethasone in the postamendment cohort abrogated IL-6 production more than four-fold ($P < .001$; Fig 1). Prophylactic pegfilgrastim on day 16 allowed patients to recover their absolute neutrophil count adequately to receive therapy as scheduled on day 1 of the following cycle.

Response

All 64 patients were evaluated for response. Thirty-four patients (53%; 95% CI, 41% to 65%) responded to therapy, including 11 (41%) of 27 preamendment, three (60%) of five transitional, and 20 (63%) of 32 postamendment patients. Responses included 30 partial responses (PRs; 47%), three nodular PRs (nPRs; 5%), and one com-

Table 3. Overall Response Rate According to Absence or Presence of High-Risk Factors

Baseline Characteristic	Response* (% of patients)		Difference (%)	95% CI (%)
	No	Yes		
Bulky lymphadenopathy	59	51	+8	-21 to +36
del(17p13)	51	57	-6	-33 to +21
del(11q22)	56	50	+6	-20 to +31
Complex karyotype†	57	48	+9	-17 to +34

*Includes complete remission, nodular partial remission, and partial remission.

†Defined as three or more cytogenetic aberrations.

Table 4. Variables Associated With Overall Response Rate

Variable	Full Model			Final Model		
	OR	95% CI	P	OR	95% CI	P
Treatment cohort: postamendment v preamendment	2.2	0.6 to 8.1	.22	—	—	—
WBC: increased two-fold	1.3	0.9 to 1.7	.14	—	—	—
Sex: female v male	4.9	1.2 to 19.4	.02	4.9	1.4 to 17.6	.01
No. of prior therapies: increase of 1	0.9	0.6 to 1.2	.33	—	—	—

NOTE. The following variables were evaluated in univariate logistic regression models for outcome: treatment cohort; age; sex; No. of prior therapies; fludarabine-refractory status; Rai stage; bulky lymphadenopathy; baseline WBC, lactate dehydrogenase, and β_2 -microglobulin levels; and presence of high-risk genetic features [ie, del(17p13.1), del(11q22.3), or complex karyotype]. Variables for which $P < .20$ in univariable models were further evaluated in a full multivariate model. The final model, after backward selection, is shown.

Abbreviation: OR, odds ratio.

to undergo allogeneic SCT. All patients initially responded to SCT, although the majority has subsequently experienced relapse. Interestingly, one patient who experienced treatment failure with allogeneic SCT received flavopiridol again and achieved an MRD-positive CR. No increased risk of graft-versus-host disease or other toxicity was observed with subsequent SCT. Of the remaining 27 responders, 20 experienced relapse or died. With a median follow-up time of 8 months, the estimated median PFS for responders was 12 months (95% CI, 8.5 to 13.1 month) and did not differ significantly according to genomic risk group, although CIs were too wide to draw strong conclusions about equality of PFS between groups (Table 5). Excluding the seven responders who underwent allogeneic SCT, the estimated median PFS was 10 months (95% CI, 8.5 to 13.1 months); again, PFS did not differ according to genomic risk group (data not shown).

DISCUSSION

This large phase II study demonstrates the significant clinical activity of flavopiridol in patients with relapsed, heavily pretreated, genetically

high-risk CLL. The response rate was not affected by the presence of high-risk genomic features or bulky lymphadenopathy. Interestingly, 77% of women responded to therapy, compared with 40% of men, and sex was the most significant variable for response in a multivariable model. We have not identified any reason for this striking sex difference in response. In contrast to the phase I study, we observed one CR and three nPRs in the phase II trial, including one patient who achieved MRD negativity and remains in CR 22.5 months after starting therapy. Furthermore, seven patients who were previously not candidates for allogeneic SCT as a result of bulky adenopathy achieved a PR/nPR and were able to undergo transplantation. A recent long-term follow-up of nonablative allogeneic SCT in CLL demonstrated the long-term benefit of SCT and a high relapse frequency in patients with bulky lymph nodes.²⁹ Thus, the ability of flavopiridol to effectively reduce bulky lymph nodes in genetically high-risk CLL patients who are resistant to other therapies represents a potential modality to allow curative application of nonablative SCT in poor-risk patients.

Although TLS was problematic in our phase I study,²⁷ our phase II findings demonstrated that limiting the pretreatment WBC to less than $200 \times 10^9/L$ lessens this toxicity. Specifically, three patients (5%) required transient hemodialysis with their first flavopiridol treatment, but all were able to continue treatment and ultimately responded to therapy. Although the vast majority of patients who receive flavopiridol do not require dialysis, the ability to perform hemodialysis emergently is required for safe administration of this drug. Thus, although specialized hematology centers may be required for the first one or two doses of flavopiridol, transition to outpatient clinics after the initial two doses seems safe and feasible.

The most common adverse events observed with flavopiridol were CRS, fatigue, anorexia, diarrhea, nausea, and vomiting. We attempted to identify the etiology of the CRS and subsequently improve the tolerability of treatment. IL-6 release had previously correlated with CRS in patients with solid tumor receiving flavopiridol.³⁰⁻³⁵ Therefore, we administered dexamethasone with each flavopiridol treatment to reduce IL-6 release and CRS symptoms. Our amendment successfully improved treatment tolerability, patient compliance, and clinical response. This study emphasizes the importance of performing phase II trials to confirm the toxicity and clinical activity observed in initial phase I trials and underscores the need to continually modify treatment regimens based on clinical observations. The use of prophylactic corticosteroids raises the possibility that corticosteroid effect may have contributed to the increased response rate observed in the post-treatment cohort, although there is no way to determine the therapeutic contribution of corticosteroids.

We prospectively sought to determine the activity of flavopiridol in genetically high-risk patients, and our results demonstrated impressive response rates and PFS in patients with del(17p13.1) and other high-risk chromosomal abnormalities who respond poorly to conventional therapies and have limited therapeutic options.³¹⁻³⁵ Although alemtuzumab is effective in this population,^{7,36} alemtuzumab is less effective against lymph nodes larger than 5 cm and is profoundly immunosuppressive.^{2,37} In contrast, we previously demonstrated that flavopiridol causes transient neutropenia but not T-cell suppression,²⁶ and the phase II trial did not observe opportunistic infections such as fungus or cytomegalovirus. Furthermore, flavopiridol is efficacious in patients with bulky lymphadenopathy, in contrast to the limited activity of alemtuzumab in this patient group. Thus, flavopiridol offers several distinct therapeutic advantages for heavily pretreated patients

Table 5. PFS of Responders According to Absence or Presence of High-Risk Factors

Baseline Characteristic	PFS (months)		Hazard Ratio*	95% CI
	Median	95% CI		
del(17p13)			0.94	0.36 to 2.48
Absent	10.3	7.2 to 13.1		
Present	12.1	9.9 to 17.2		
del(11q22)			1.83	0.74 to 4.53
Absent	12.1	8.5 to 18.6		
Present	9.9	6.6 to 13.1		
Complex karyotype†			1.04	0.41 to 2.64
Absent	10.3	8.5 to 13.1		
Present	12.1	7.1 to 17.2		

Abbreviation: PFS, progression-free survival.

*A hazard ratio > 1.00 or < 1.00 indicates an increased or decreased risk, respectively, of progression in patients with the presence of a high-risk factor.

†Defined as three or more cytogenetic aberrations.

with relapsed CLL who often have high-risk cytogenetic features, bulky lymph nodes, and profound cellular immunosuppression. Flavopiridol achieves durable remissions in these high-risk patients, and our phase II results indicate that flavopiridol can serve as an effective bridge to a potentially curative nonablative allogeneic SCT.

In summary, we have demonstrated the clinical activity of flavopiridol in refractory CLL and prospectively validated its efficacy in genetically high-risk disease including del(17p13.1). Future development of flavopiridol using the amended schedule outlined herein in CLL and other related lymphoid malignancies is indicated. Although TLS may not be the DLT in other malignancies, myelosuppression may limit dose escalation in other diseases. Finally, although flavopiridol shows significant single-agent activity in CLL, consideration should be given to combination regimens in other diseases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory**

Role: Thomas S. Lin, sanofi-aventis (C); Michael R. Grever, sanofi-aventis (U); John C. Byrd, sanofi-aventis (U) **Stock Ownership:**

None **Honoraria:** Thomas S. Lin, sanofi-aventis **Research Funding:** Thomas S. Lin, sanofi-aventis **Expert Testimony:** None **Other Remuneration:** Thomas S. Lin, Michael R. Grever, John C. Byrd

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Financial support: Thomas S. Lin, Miguel A. Villalona-Calero, Michael R. Grever, John C. Byrd

Administrative support: Beth Fischer, Sarah M. Mitchell, Miguel A. Villalona-Calero, Michael R. Grever, John C. Byrd

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