Flavopiridol treatment of patients aged 70 or older with refractory or relapsed chronic lymphocytic leukemia is a feasible and active therapeutic approach

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ABSTRACT

Older chronic lymphocytic leukemia patients have poor outcomes with standard treatments and are underrepresented in clinical trials. We retrospectively reviewed outcomes of refractory chronic lymphocytic leukemia patients in two age categories (≥70 and <70 years) treated with single-agent flavopiridol, a drug active in genomically high-risk patients, during two trials. No significant difference between older and younger patients was observed in response rates (43 *vs.* 47%) or progression-free survival (median 8.7 *vs.* 9.9 months, P>0.80). Although overall survival was worse in older patients (median 2.1 *vs.* 2.4 years, P=0.02); when adjusted for other factors this difference was no longer significant (P≥0.10). With the exception of infections (older 29% vs. younger 62%) no significant association with toxicity was observed. These data demonstrate that flavopiridol administration to older chronic lymphocytic leukemia patients is feasible, tolerable, and may have similar efficacy to that in younger patients. Development of treatment approaches including flavopiridol should be considered for these older patients.

Key words: chronic lymphocytic leukemia, elderly, flavopiridol, refractory, relapsed.

Citation: Stephens DM, Ruppert AS, Blum K, Jones J, Flynn JM, Johnson AJ, Ji J, Phelps MA, Grever MR, and Byrd JC. Flavopiridol treatment of patients aged 70 or older with refractory or relapsed chronic lymphocytic leukemia is a feasible and active therapeutic approach. Haematologica 2012;97(3):423-427. doi:10.3324/haematol.2011.047324

Introduction

Although the most rapidly growing portion of the United States population is the elderly, they are consistently underrepresented in clinical cancer trials.[1] The incidence of chronic lymphocytic leukemia (CLL) is markedly increased in older people, with a median age at diagnosis of 72 years. In fact, 75% of CLL patients in the United States are over the age of 65 years and 50% are over the age of 75 years.[2] In contrast, key trials to evaluate the first-line treatment for CLL enrolled patients with a median age between 58 and 66 years.[3] Studies focused on older CLL patients have been limited. For example, whereas first-line fludarabine was shown to be a superior therapy to chlorambucil,[4] its benefit to patients aged 65 and older was not observed in a recently reported randomized phase III study.[5] The benefit of first-line chemoimmunotherapy with the addition of rituximab has improved outcome of CLL patients but this benefit was less appreciated in patients over the age of 70 (n=30 of 224).[6] A phase III clinical trial demonstrated that among 245 patients aged older than 65 (n=81, ≥70), response rate was improved and time to progression was extended in those that received first-line chemoimmunotherapy with rituximab *versus* those who received front-line chemotherapy, although no significant improvement in overall survival was observed. These older patients had higher incidences of at least one grade 3 or 4 toxicity, notably hematologic toxicity and bacterial infections, when compared with the patients under the age of 65.[7] In the therapy of relapsed CLL, even less is known about the impact of age. However, one study in relapsed CLL with fludarabine, cyclophosphamide, and rituximab (n=177, median age=59 years, range=36-81 years) demonstrated a significant association between younger age and complete response rates, indicating less benefit of this treatment regimen in elderly patients.[8] Collectively, these studies emphasize the importance of considering age and independent assessment of the feasibility of administration of new therapeutic agents in older patients.

Flavopiridol, is a pan cyclin-dependent kinase inhibitor[9] which has demonstrated noteworthy clinical activity in relapsed and refractory CLL patients including those with del(17p13.1).[10-11] The common side effects observed with flavopiridol, including hyperacute tumor lysis syndrome (TLS), cytokine release syndrome (CRS), neutropenia, diarrhea and fatigue, are often seen but are manageable. Given the activity of single-agent flavopiridol in relapsed CLL, we sought to determine the feasibility and impact of treating patients aged 70 or

*These two senior authors contributed equally to this work.

Funding: the authors would like to thank the Leukemia and Lymphoma Society SCOR grant, the D Warren Brown Foundation, NIH/NCI; P01 CA81534, and 5KL2RR025754-02, 5K12 CA133250-03, N01-CM-62207, and U01 CA 076576. AJ is a Paul Calabresi Scholar.
Manuscript received on May 16, 2011. Revised version arrived on September 12, 2011. Manuscript accepted on October 13, 2011.
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older in this setting by retrospectively reviewing outcome of such patients enrolled on 2 clinical trials at our institution.

Design and Methods

Patients and treatment

Patients included in this study were enrolled on two National Cancer Institute (NCI)-sponsored and Ohio State University (OSU) institutional review board (IRB)-approved trials. All patients provided written informed consent. Patient enrollment criteria included: age older than 17 years; diagnosis of CLL, prolymphocytic leukemia arising from CLL, or small lymphocytic lymphoma; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; and serum creatinine and total bilirubin levels lower than 2 times the normal value. The combined total of 116 patients was then divided by age into 2 categories (≥70 years and <70 years) for comparison. Traditionally, most studies define *elderly* as over the age of 65. However, as mentioned previously, CLL is diagnosed at a median age of 72 years and 50% of CLL patients in the United States are over the age of 75.[2] Thus, we chose to use 70 as the cut-off point, better defining the *elderly* population of CLL patients. The distinct treatment and prophylactic treatment regimens have been summarized previously.[10-12]

Toxicity and response assessment

Toxicity was assessed by the NCI Common Toxicity Criteria of Adverse Events (version 3) and modified NCI Common Toxicity Criteria guidelines for evaluating hematologic toxicity in leukemia. Patients were assessed for clinical response by the 1996 NCI Working Group response criteria[13] after two, four, and six cycles. Progression-free survival (PFS) was calculated from the date of registration to time of disease progression or death, whichever occurred first. Patients were censored for PFS at the time last known to be progression-free, next treatment, or stem cell transplantation. Overall survival (OS) was calculated from the date of registration to the date of death, censoring patients alive at last follow up.

Statistical analysis

The primary aims were to assess differences in pre-treatment characteristics, treatment tolerability, and clinical outcome between patients aged at least 70 and younger patients. Associations between age groups and categorical or continuous variables were described using Fisher's exact or Wilcoxon's rank sum tests, respectively. Estimated probabilities of PFS and OS were calculated by the Kaplan-Meier method, and the log rank test evaluated differences between survival distributions. Logistical regression and proportional hazards models were used to evaluate the impact of age group on response or PFS and OS, respectively, when controlling for variables deemed *a priori* to be most important; the models were not developed using an automated selection procedure. Hence, all models were controlled for treatment dose/schedule and Rai stage, as well as presence of complex karyotype, a variable associated with both increased age and clinical outcome. Statistical significance was set at alpha = 0.05.

Results and Discussion

Patients' characteristics

A total of 116 patients were enrolled in the two studies, with a median age of 60 years (range 31-84). Of those, 95 (82%), were younger than 70 years of age and 21 (18%) were aged 70 or older. For most pre-treatment characteristics as summarized in Table 1, there was no great difference between older and younger patients. However, older patients presented more frequently (63 *vs.* 37%, *P*=0.04) with complex karyotype (three or more cytogenetic aberra-

Table 1.

Characteristic	Age < 70 n = 95	Age ≥ 70 n = 21	P
Study			0.48
OSU0055	41 (43)	11 (52)	
OSU0491	54 (57)	10 (48)	
Treatment dose/schedule*, n. (%)			0.05
Initial Phase I	16 (17)	7 (33)	
Modified Phase I and Phase II	49 (52)	12 (57)	
Dose Escalation Amended Phase II	30 (32)	2 (10)	
Sex			0.80
Male	66 (69)	14 (67)	
Female	29 (31)	7 (33)	
Rai stage, n. (%)			0.07
I/II	23 (24)	1 (5)	
III/IV	72 (76)	20 (95)	
Bulky lymphadenopathy ≥ 5 cm, n. (%)			1.00
No	24 (25)	5 (24)	
Yes	71 (75)	16 (76)	
Purine analog refractory, no. (%)			0.78
No	24 (25)	4 (19)	
Yes	71 (75)	17 (81)	
Dohner prioritization[24]			0.30
Del(17p)	31 (33)	9 (47)	
Del(11q)	31 (33)	6 (32)	
Trisomy 12	7 (8)	2 (11)	
No detected aberrations	15 (16)	0 (0)	
Del(13q)	9 (10)	2 (11)	
Complex karyotype**			0.04
No	59 (63)	7 (37)	
Yes	34 (37)	12 (63)	
Number of prior treatments, n. (%)			0.69
Median	5	4	
Range	1-14	1-8	
Completed all treatment			1.00
No	76 (80)	17 (81)	
Yes	19 (20)	4 (19)	
Response,[13] n. (%)			0.96
CR	1 (1)	0 (0)	
nPR	3 (3)	0 (0)	
PR	41 (43)	9 (43)	
SD	12 (13)	3 (14)	
NR	38 (40)	9 (43)	
Progression-free survival (PFS)			0.86
Median, years	0.8	0.7	
%PFS at 2 years (95% CI)	11 (5-21)	5 (<1-22)	
Overall survival (OS)			0.02
Median, years	2.4	2.1	
%OS at 2 years (95% CI)s	56 (45-66)	52 (30-71)	

**Initial Phase I dose group included the first two cohorts of OSU-0055 and consisted of 30 mg/m² 30-minute intravenous bolus dose (IVB) +30 mg/m² 4 h continuous intravenous infusion (CIVI) (n=20) or 40+40 (n=3).The modified Phase I and Phase II dose group included cohorts 3 (n=17) and 4 (n=12) of OSU-0055 and the first cohort (n=27) of OSU-0491. These patients received 30 mg/m² IVB +30 mg/m² CIVI followed by 30 mg/m² IVB + 50 mg/m² CIVI. Doses were given weekly for four weeks followed by two weeks off for up to six cycles. The Dose Escalation Amended Phase II group (n=32) included patients from the second cohort of OSU-0491 with patients receiving 30 mg/m² IVB +30 mg/m² CIVI followed by 30 mg/m² IVB + 50 mg/m² CIVI. Doses were given weekly for three weeks followed by one week off for a reduced number of cycles and with steroids in order to increase treatment tolerability. Five patients on OSU-0491 started in cohort 1 and were transitioned to cohort 2 during the study.[14] **Defined as 3 or more cytogenetic aberrations.*

tions on stimulated metaphase karyotype), and with advanced Rai stage III/IV (95 *vs.* 76%, *P*=0.07) compared to younger patients. Lastly, the two groups of patients were non-randomly distributed among the treatment doses/schedules of flavopiridol (*P*=0.05); just over half of younger and older patients received 30+30 mg/m^2 of flavopiridol followed by 30+50 mg/m^2, whereas a smaller proportion of older patients received this dose with an amended schedule aimed at improving tolerability, and a higher proportion of older patients received either 30+30 mg/m^2 or 40+40 mg/m^2 without the intrapatient dose escalation. However, even with this discrepancy, there was no significant difference in the median number of cycles of flavopiridol received (*P*=0.69) or the proportion of patients who completed all therapy (*P*=1.00; Table 1).

Toxicity

Common toxicities including TLS, CRS, infection, and hematologic toxicities, anemia, neutropenia, and thrombocytopenia were examined between the groups and are summarized in Table 2. We noted no significant associations between age group and grade of toxicity, with the exception of infection (*P*=0.03). Only 29% of older patients experienced infection with one grade 5 (patient age=82 years), 2 grade 3, and 3 grade 2 infections, as compared with 62% of younger patients.

Response, progression-free survival (PFS), overall survival (OS)

No significant difference was observed in response rates, with 43% of older patients achieving response *versus* 47% of younger patients (odds ratio=0.8, 95% CI: 0.3-2.2) (Table 1). All responses were partial or nodular partial remissions, except for a 67-year old patient who achieved a complete remission. The estimated median PFS for older and younger patients was 8.7 and 9.9 months, respectively (hazard ratio (HR)=1.0 [95%CI: 0.6-1.7]; Table 1; Figure 1A). There remained no significant differences in response rates or PFS when controlling for treatment dose/schedule, Rai stage and presence of complex karyotype (*P*=0.76 and *P*=0.93, respectively). Although OS was shorter in older patients compared with younger patients (HR=1.8 [95%CI: 1.1-2.9]; Figure 1B), following adjustment for Rai stage, the higher risk due to older age was lessened (HR=1.5 [95%CI: 0.9-2.5], *P*=0.10) and diminished further when also controlling for treatment dose/schedule and presence of complex karyotype (HR=1.2 [95% CI: 0.7–2.1], *P*=0.54).

Discussion and Results

We demonstrate that the cyclin-dependent kinase inhibitor flavopiridol is highly active in the treatment of older CLL patients (≥70 years). We demonstrate no significant difference in toxicity, response, or PFS in older patients compared to younger patients enrolled on two sequential phase I/II flavopiridol trials performed at our institution.[10, 11] Of 27 patients censored for PFS (n=2 aged 70 or older and n=25 younger than 70 years), 7 went off-study to receive transplant and one patient remains progression-free and alive at 2.7 years after going on study (age=39 years). Most of the remaining censored patients had stable disease with continued symptoms and went off-study to receive other therapies. With respect to OS, there have been 86 deaths with 30 patients younger than 70 years of age alive at last follow up. Although OS was shorter in older patients, older age tended to be associated with adverse risk factors Rai stage III/IV (*P*=0.07) and complex karyotype (*P*=0.04). Furthermore, only 2 of the older patients were treated on the amended dose escalation schema of the phase II clinical trial, where number of weekly treatments per cycle was reduced from four to three and prophylactic dexamethasone was added to improve treatment tolerability and delivery. When controlling for these three factors, older age no longer provided a significant amount of information in explaining survival (*P*=0.54), albeit the wide confidence interval on the risk of death included hazard ratios as little as 0.7 but as high as 2.1.

The older population is the most rapidly growing population in the United States and the incidence of CLL is markedly increased in these patients[2] with a disproportionate lack of representation of these patients in clinical trials.[3] Given that flavopiridol has demonstrated class-specific dose limiting toxicities of hyperacute TLS and CRS, concern for feasibility in older patients might be raised. However, in this study, there was no difference in the number of flavopiridol cycles received and the proportion of patients who completed all cycles of therapy between older and younger patients. In addition, in this study there were no significant associations between age group and grade of common toxicities, with the exception of infection (*P*=0.03), where older patients experienced less infection than younger patients (29% *vs.* 62%). We considered that older patients may have experienced fewer infections due to the pharmacokinetics (PK) of flavopiridol or its glucuronide metabolite (flavo G) (sample preparation and metabolite quantification as previously described).[12,15]

Table 2. Toxicity of 116 CLL patients according to age.

Toxicity	Age < 70 n = 95	Age ≥ 70 n = 21	*P*
TLS			1.00
None	52 (55)	11 (52)	
Grades 1-2	0 (0)	0 (0)	
Grades 3-5	43 (45)	10 (48)	
CRS			1.00
None	61 (64)	14 (67)	
Grades 1-2	27 (28)	6 (29)	
Grades 3-5	7 (7)	1 (5)	
Infection			0.03
None	36 (38)	15 (71)	
Grades 1-2	28 (29)	3 (14)	
Grades 3-5	31 (33)	3 (14)	
Anemia			0.55
None	36 (38)	6 (29)	
Grades 1-2	51 (54)	12 (57)	
Grades 3-5	8 (8)	3 (14)	
Neutropenia			0.50
None	10 (11)	3 (14)	
Grades 1-2	7 (7)	0 (0)	
Grades 3-5	78 (82)	18 (86)	
Thrombocytopenia			0.57
None	30 (32)	6 (29)	
Grades 1-2	36 (38)	6 (29)	
Grades 3-5	29 (31)	9 (43)	

One grade 5 TLS was observed in a 44-year old patient enrolled in the second cohort of the Phase I study (here presented as original dosing schema). There were 5 patients with grade 5 infection with ages 47, 52, 58, 68, and 82.

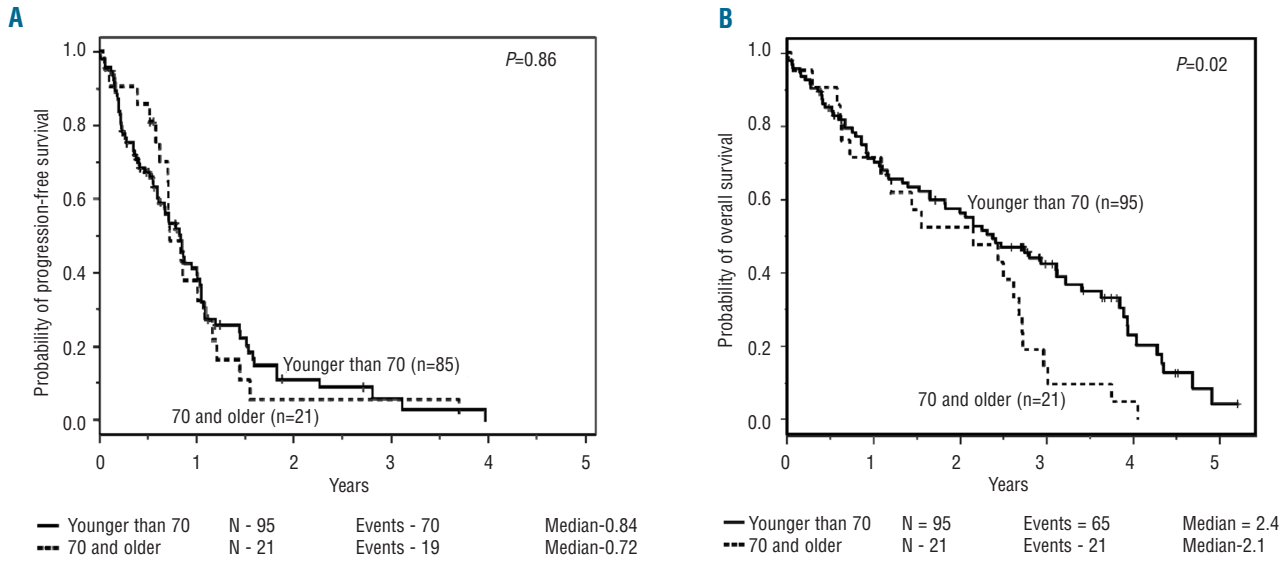

Figure 1. (A) **Progression-free survival following treatment with flavopiridol dichotomized by age <70 or ≥70 years and** (B) **overall survival following treatment with flavopiridol dichotomized by age <70 or ≥70 years.**

However, a review of the PK data showed no significant differences in PK parameter estimates between the two age groups (*data not shown*). Thus, it is unclear why older patients had fewer infections with flavopiridol and this is currently being investigated at our institution. Nevertheless, these data collectively provide support that flavopiridol can be administered in older patients just as safely as in younger patients.

Other trials and reports of new therapeutic approaches have only paid minimal attention to the impact of age on outcome. For example, several recent trials studying lenalidomide, an immunomodulatory analog of thalidomide, have shown promising results for this drug in relapsed CLL with high-risk cytogenetic features. Two phase II studies evaluating lenalidomide in 45 and 44 relapsed CLL patients demonstrated overall response rates of 47 and 32%, respectively, with complete remission rates of 9 and 7%, respectively.[16-17] Unfortunately, the former study only included 12 patients over 70 years of age and the second study reported a median age of 64, but did not specifically detail the ages of the patients or the impact of age on outcome. The pivotal study of ofatumumab included 138 patients with CLL who were either refractory to both fludarabine and alemtuzumab or fludarabine-refractory with bulky lymphadenopathy (>5cm) and demonstrated OR rates of 58 and 47%, respectively;[18] only 10 patients (7%) were over the age of 70. Furthermore, the interim analysis of a large multicenter phase II study of flavopiridol in patients with fludarabine-refractory CLL, which demonstrated a 31% OR rate, included patients with a median age of 61 years;[19] much below our targeted population of patients over the age of 70. Similarly, recent phase I and II trials targeting Bcl-2 with oblimersen,[20] obatoclax,[21] and ABT-263,[22] have also included few older patients and have not examined the impact of age on outcome in any depth.

Our retrospective study is also limited by its small number of patients seen at a single institution, meaning that definitive conclusions cannot be drawn from the data. In addition, the enrollment criteria required the patients to have an ECOG performance status of 2 or less, which may add bias by including patients who are fitter than those seen in the general CLL population. Previous analysis has shown a trend towards inferior survival in non-Hodgkin's lymphoma patients with a higher comorbid disease burden.[23] As our study was not designed to identify differences between the older and younger groups, a comorbidity index, such as the Sorror version of the Charlson Index,[24] was not calculated as a part of the patients' baseline characteristics. The use of a comorbidity index would be required to provide more information about the safety of flavopiridol administration to patients with a higher comorbid disease burden.

In summary, our study demonstrates that flavopiridol administration to older CLL patients is both feasible and acceptably tolerated relative to younger patients. When controlling for the fact that older patients presented with more aggressive disease, increased age in itself did not appear to be associated with inferior efficacy of flavopiridol. Although our results are based on a relatively small cohort of patients aged 70 and older, there is currently no strong evidence that these older patients cannot tolerate or respond favorably to treatment with flavopiridol. Hence, future development of treatment approaches with both single-agent and combination strategies of flavopiridol should be considered for older CLL patients.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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