Leukemia Research 37 (2013) 1195–1199

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Cyclophosphamide, alvocidib (flavopiridol), and rituximab, a novel feasible chemoimmunotherapy regimen for patients with high-risk chronic lymphocytic leukemia

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ARTICLE INFO

Article history:
Received 4 April 2013
Received in revised form 22 May 2013
Accepted 5 June 2013
Available online 15 July 2013

Keywords:
Chronic lymphocytic leukemia
Flavopiridol
High-risk cytogenetics
Cyclin-dependent kinase inhibitor
Chemoimmunotherapy
Alvocidib
Del(17p)
Del(11q)

ABSTRACT

Alvocidib has demonstrated efficacy in high-risk chronic lymphocytic leukemia (CLL) patients. In this phase I study, we combined cyclophosphamide, alvocidib and rituximab (CAR) in a schema designed to mitigate tumor lysis syndrome (TLS) seen previously with alvocidib. Nine nucleoside analog-naïve, high-risk patients received escalating doses of CAR therapy. Dose limiting toxicity was not experienced. No instances of TLS were observed. Patient responses included three complete remissions and four partial remissions. CAR was tolerable and active in high-risk CLL patients without TLS toxicity. With continued monitoring of toxicities, a phase Ib/II study of this combination as frontline therapy is warranted.

1. Introduction

Despite significant changes and progress in the treatment of chronic lymphocytic leukemia (CLL) patients, specific genomic [del(17p13.1), del(11q22.3), un-mutated immunoglobulin heavy chain variable region (IgV_H)] and clinical [age ≥ 70 years and β2microglobulin (B2M) level ≥ 4] risk factors continue to be associated with poor clinical outcomes [1,2]. Chemoimmunotherapy has become the standard of care in frontline CLL therapy secondary to improvements in progression-free survival (PFS) and overall survival (OS) [3]. However, standard regimens are not curative and efforts are ongoing to optimize therapy for CLL patients.

In contrast to standard chemoimmunotherapies, alvocidib (flavopiridol), a cyclin-dependent kinase (CDK) inhibitor, has been shown to be effective in high-risk groups of CLL patients and does not promote the same cellular immune suppression typically seen with chemotherapy agents, such as fludarabine. Combined analysis of two early clinical phase I/II trials of alvocidib [4–6] included 112 heavily pre-treated patients [36% with del(17p13.1) and 33% with del(11q22.3)] demonstrated an impressive overall response rate (ORR) of 46% and a median progression-free survival (PFS) of approximately 10 months. There were no significant differences in ORR or PFS among cytogenetic groups [7] or in patients older

Abbreviations: B2M, beta 2 microglobulin; CAR, cyclophophamide, alvocidib, rituximab; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; CR, complete response; CRS, cytokine release syndrome; DLT, dose limiting toxicity; ECOG, Eastern Cooperative Oncology Group; FC(R), fludarabine, cyclophosphamide, (rituximab); IgV_H, immunoglobulin heavy chain variable region; MTD, maximum tolerated dose; NCI, National Cancer Institute; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; ORR, overall response rate; OS, overall survival; TLS, tumor lysis syndrome; WBC, white blood cell.

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http://dx.doi.org/10.1016/j.leukres.2013.06.006

Table 1
Dose escalation schema for cyclophosphamide, alvocibib, and rituximab regimen.

Cohort	Rituximab	Cyclophosphamide	Alvocidib
1. ($n=3$)	100 mg IV C1D1; 375 mg/m^2 IV C1D2 and C2-6D1	300 mg/m^2 IV C1-6D1-3	30 mg/m^2 IV (30 min), 30 mg/m^2 IV (4 h) C1D8; C2-6D1 and 8
2. ($n=3$)			30 mg/m^2 IV (30 min), 50 mg/m^2 IV (4 h) C1D8, C2-6D1 and 8
3. ($n=3$)		375 mg/m^2 IV C1-6D1-3	

IV, intravenous; C, cycle, D, day.

versus younger than age 70 [8], suggesting efficacy of alvocidib in these high-risk populations.

However, during the phase I trials, the dose limiting toxicity (DLT) of alvocidib was hyperacute tumor lysis syndrome (TLS), occurring in 48% of patients, with 19% requiring dialysis [9]. To limit TLS, eligibility was modified in the phase II trial [6], by restricting enrollment to patients with white blood cell (WBC) count $<200 \times 10^9$/L, implementing aggressive TLS prophylaxis, and reducing cycle length and number of treatments per cycle. With these modifications, more patients completed therapy, and the severity of TLS decreased. The overall rate of TLS on the phase II trial was 44% with 6% requiring dialysis. TLS occurred most frequently in patients with Rai Stage III/IV, female gender, adenopathy ≥ 10 cm, elevated WBC count, increased B2M, decreased albumin, and higher plasma levels of alvocidib–glucuronide (a glucuronidated metabolite of alvocidib) [9].

Concerns related to the onset of acute TLS portends to a potential limitation to its use. Therefore, we combined cyclophosphamide, alvocidib, and rituximab (CAR) with the aims of developing an effective regimen for high-risk CLL patients, while limiting toxicities and demonstrating potential feasibility of administration as an out-patient.

2. Materials and methods

2.1. Patients

Patients were enrolled on the National Cancer Institute (NCI)-sponsored and The Ohio State University institutional review board-approved study following written informed consent. Enrollment criteria included: age over 17 years, symptomatic CLL or SLL by NCI criteria [1] with poor-risk genetic or clinical risk factors [presence of del(17p13.1), del(11q22.3), unmutated IgV_H ($\geq$98% homology), age over 70 years and/or elevated B2M ($\geq$4)], no prior therapy with purine analogs, Eastern Cooperative Oncology Group (ECOG) [10] performance status less than 3, no active infection, and adequate renal and hepatic function. Patients with cytopenias were not excluded from participation.

2.2. Study design, treatment plan, and dose escalation schema

The study was designed as a traditional 3×3 phase I model, where 3–6 patients were enrolled at each dose level. The maximum tolerated dose (MTD) was defined as the dose level below which 2 or more of a cohort of 6 patients experienced dose-limiting toxicity (DLT), as defined in the following section. At the MTD, the study initially planned for an expansion cohort of 12 patients for a total of 18 patients treated for further evaluation of safety for phase II trials. Table 1 provides a detailed dose schedule description for each cohort.

2.3. Dose limiting toxicity

DLT was defined as the occurrence of any of the following events during the first two cycles of therapy when judged to be clinically significant (as further defined below) and possibly, probably, or definitely related to the study treatment. Adverse events that were clearly the result of disease progression, concomitant medical illness, or accidental injury were not considered DLT. Toxicity grading was performed using the CTEP Active Version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) [11]. DLT for this study was defined as follows: (1) any grade 3 or 4 non-hematologic toxicity (with the exceptions of: reversible electrolyte or glucose abnormalities, liver function test abnormalities that returned to $\leq$grade 2 in <5 days, and TLS not requiring dialysis); (2) grade 3 or 4 hematologic toxicity that did not resolve to 20% of baseline by day 35 of therapy (unless disease-related); and (3) grade 3 infection or febrile neutropenia.

2.4. Supportive care

All patients received allopurinol (300 mg daily) for the duration of the trial. For the first 2 doses of alvocidib, patients received inpatient pretreatment hydration, urine alkalization, and prophylactic phosphate binder therapy, rasburicase (4.5 mg) 2 h prior to dose. Other supportive care measures were as detailed in previous reports [4,6].

2.5. Response assessment

International Workshop on Chronic Lymphocytic Leukemia Guidelines [1] were used for assessment of response. For patients not demonstrating disease progression, response status was evaluated after Cycles 2, 4, and 6 (if applicable) and 2 months following therapy completion.

2.6. Pharmacokinetics

Plasma pharmacokinetics (PK) of alvocidib and alvocidib-glucuronide were assessed in each patient on Day 8 of both Cycles 1 and 2. Plasma samples were collected pre-dose and at 0.5, 4.5 and 24 h after the start of alvocidib infusion. PK samples were analyzed using methods as described previously [12,13]. Non-compartmental PK parameters were determined for alvocidib and alvocidib-glucuronide in Phoenix WinNonlin v.6.3. Population PK parameter estimates for both agents were determined by incorporating plasma concentration data versus time, body weight, and sex from this study into a previous dataset and population PK/pharmacodynamic model for alvocidib-induced TLS [14].

2.7. Statistics

The primary endpoint of the study was to define the MTD of CAR, using the traditional 3×3 phase I design as described above in the Section 2.2. Secondary endpoints included describing response rates, PFS, and OS following administration of CAR. Common hematologic and non-hematologic toxicities are summarized with frequencies by dose level and for all patients. Baseline characteristics are described using frequencies and medians with ranges for categoric and continuous variables, respectively. PFS was measured from the date of first treatment to the date of progression or death from any cause, censoring patients alive at last follow-up. OS was measured from the date of first treatment to the date of death or date of last follow-up. Best response, PFS, and OS are provided for each patient. Observed PK parameters were evaluated and summarized in graphic and table format. No inferential statistical tests of hypotheses were planned due to the small sample size.

Table 2
Pretreatment patient characteristics.

Characteristic	Patients ($n=9$)
Median age in years (range)	55 (43–77)
Male	7
Caucasian	8
ECOG performance status [10]	
0	7
1	2
Number of prior treatments	
0	6
1	2
2	1
Rai stage at treatment	
Intermediate risk (I–II)	7
High risk (III–IV)	2
Del(17p)	3
Del(11q)	4
Complex cytogenetics	3
Unmutated IgV_H status ($n=7$)	6
β2microglobulin > 4	1
Bulky adenopathy > 5 cm	0
Median leukocyte count $\times 10^9$/L (range)	66.9 (3.4–217.0)
Median hemoglobin, g/dL (range)	11.8 (9.5–14.2)
Median platelet count $\times 10^9$/L	138 (75–250)