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Low efficacy and high mortality associated with clofarabine treatment of relapsed/refractory acute myeloid leukemia and myelodysplastic syndromes

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ABSTRACT

Clofarabine, a second-generation nucleoside analog, has clinical activity in relapsed or refractory acute myelogenous leukemia (AML) and higher-risk myelodysplastic syndromes (MDS). However, there are few data evaluating performance of clofarabine in populations of patients not enrolled in clinical trials. We reviewed outcomes for 84 patients treated with clofarabine for relapsed or refractory AML or MDS, either with clofarabine as monotherapy ($n = 19$) or in combination with cytarabine ($n = 65$). Using International Working Group (IWG) response criteria, the overall response rate (ORR) of all treated patients was 21%, with a complete response rate with either complete or incomplete hematopoietic recovery (CRR = CR + CRi) of 14%. For combination therapy, ORR was 22% with CRR of 18%, and monotherapy patients had an ORR of 21% with CRR of 11%. Although limited by small numbers, subgroup analysis did not reveal variation in response rates when comparing different risk factors. The 30-day mortality was 21% and median survival was 3 months; a subset of 12 patients who were able to go to transplant had an 18-month median survival. Clofarabine's efficacy in a "real-world" setting appears to be less than has been reported in clinical trials, and treatment is associated with a high early mortality rate.

1. Introduction

Clofarabine (2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine) is a second-generation halogenated deoxyadenosine nucleoside analog developed by the Southern Research Institute in the 1980s and 1990s to overcome pharmacological properties that limited effectiveness of fludarabine and cladribine in some patients with hematological malignancies [1]. A phase I study of intravenously administered clofarabine conducted at MD Anderson Cancer Center established the maximum tolerated dose for patients with hematologic and solid cancers at 40 mg/m^2/day for 5 consecutive days (dose limiting toxicity hepatotoxicity) and 2 mg/m^2/day for 5 days (dose limiting toxicity myelosuppresion), respectively [2]. Clofarabine was then investigated in pediatric patients with acute lymphoblastic leukemia (ALL), and an overall response rate of 32% in this group led to United States (US) Food and Drug Administration approval of clofarabine for a pediatric ALL indication in December 2004 [3,4]. Clofarabine's use in this population has been chiefly as a bridge to stem cell transplantation.

In the last decade, clofarabine has seen substantial off-label clinical use in the US for adult acute myeloid leukemia (AML), either as monotherapy or in combination with cytarabine, and this use is supported by National Comprehensive Cancer Network (NCCN) guidelines (category 2B designation) [5]. Investigators have examined clofarabine's role in relapsed or refractory AML in multiple phase I–II studies and a single randomized controlled trial [6]. The ranges for overall response and complete response rates assessing the combination of clofarabine with cytarabine are 40–61% and 24–46%, respectively [5,7–12]. The largest trial of clofarabine to date in the relapsed/refractory setting, CLASSIC I, was the only randomized controlled trial of this agent in the AML setting: in CLASSIC I, the combination of clofarabine and cytarabine was

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Table 1
Published clinical trials assessing clofarabine in relapsed/refractory AML.

Study	Therapy	#Patients	#OR	ORR	#CRs	CR	95% CI ORR	95% CI CRs only
Kantarjian et al. (2003)	Clo	39	21	0.54	15	0.38	.39–.68	.25–.54
Foran et al. (2003)	Clo ind + cons	40	2	0.05	0	0	.005–.17	NA
Faderl et al. (2005)[a]	Clo + Ara-C	29	12	0.41	7	0.24	.25–.59	.12–.42
Becker et al. (2011)	Clo + Ara-C + G-CSF	46	28	0.61	21	0.46	.46–.74	.32–.60
Agura et al. (2011)	Clo + Ara-C	18	7	0.39	6	0.33	.20–.61	.16–.56
Scappini et al. (2012)	Clo + HiDAC	47	29	0.62	24	0.51	.47–.74	.37–.65
Tse et al. (2011)	Clo + Ara-C	21	9	0.43	9	0.43	.24–.63	.24–.63
Faderl et al. (2012)	Clo + Ara-C vs. Ara-C	162	76	0.47	57	0.35	.39–.55	.28–.43
Meta analysis		402	184	0.46	139	0.35	.41–.51	.30–.39

Abbreviations: AML, acute myeloid leukemia; Clo, clofarabine; Ara-C, cytarabine; HiDAC, high dose cytarabine; ind, induction; cons, consolidation; NA, not applicable; #, number; ORR, overall response rate; CR, complete remission; CI, confidence interval; #OR, number of patients who were overall responders; G-CSF, granulocyte colony stimulating factor.

[a] Included four patients with high risk MDS, two with acute lymphoblastic leukemia, and one blast-phase chronic myeloid leukemia.

associated with overall and complete response rates of 47% and 35%, respectively, compared to 22% and 18% with cytarabine monotherapy. However, the CLASSIC I study, which was limited to patients with a first relapse, did not show an overall survival benefit with clofarabine [9].

There are few data assessing outcomes of clofarabine in populations treated outside the context of clinical trials. Typically in "off-study" populations, response rates to anti-neoplastic agents are lower than in the carefully selected trial population, and off-study data are valuable to have when counseling patients [13]. Additionally, treatment with clofarabine-based regimens is associated with higher drug-specific costs than several alternative regimens for patients with relapsed AML, and therefore it is important to understand response patterns to assess whether such high costs are justifiable [14]. Since clofarabine is often employed as a salvage therapy for patients who decline clinical trial participation or are ineligible for a clinical study, we examined the outcomes associated with clofarabine therapy in relapsed or refractory AML or higher-risk myelodysplastic syndromes (MDS) in this setting.

2. Materials and methods

2.1. Patients

Patients included in this analysis were those who had provided written consent for review of medical records via an Institutional Review Board-approved protocol and who were treated at Dana-Farber Cancer Institute (DFCI) or Brigham & Women's Hospital (BWH) with clofarabine for a diagnosis of AML or MDS between the drug's FDA approval in late 2004 and the end of 2013. In order to identify patients, we queried three separate databases at DFCI and BWH: the Clinical Operations and Research Information Systems (CORIS) research database, the BWH inpatient pharmacy drug administration database, and the DFCI outpatient pharmacy drug administration database.

2.2. End points and response criteria

Patient records were reviewed for overall response rate (ORR), complete response rate (CRR, which included a complete response rate with or without incomplete hematopoietic recovery), overall survival, reported adverse events, and 30-day mortality or induction death. Response rates were assessed across various subgroups (e.g., clofarabine monotherapy vs. combination therapy with cytarabine, patients with primary refractory AML vs. relapsed AML), adverse events, and characteristics of responders (e.g., karyotype, prior regimens received, pre-treatment blast proportion).

Response rates were defined per International Working Group (IWG) criteria – IWG 2003 criteria for AML and IWG 2006 criteria for MDS [15,16]. Using these criteria, complete response (CR) for AML was determined by morphologic complete remission, which requires normalization of the bone marrow ($\leq$5% blasts in a normocellular marrow) and peripheral counts with no circulating blast cells, a neutrophil count of more than or equal to 1×10^9 L^{-1} and platelet counts more than or equal to 100×10^9 L^{-1}. A CR for MDS requires the above blast criteria, as well as hemoglobin >11 g/dL and neutrophil count more than or equal to 1.5×10^9 L^{-1}. For AML, complete response with incomplete hematopoietic recovery is similar to a CR, but without recovery of platelets to more than or equal to 100×10^9 L^{-1} or neutrophils more than or equal to 1×10^9 L^{-1}. A partial response for AML consists of a blood count recovery as for CR, but with persistence of 5–25% marrow blasts with at least a 50% decrease in blasts. PR in MDS requires all CR criteria if abnormal before treatment except that marrow blasts should decrease by 50% or more compared with pretreatment levels, or a demonstration of a less advanced MDS disease classification than prior treatment. Hematologic improvement was assessed for MDS based on the IWG 2006 guidelines. For MDS, CR and PR, and HI required peripheral blood standards met for at least 8 weeks, and demonstration of at least two assessments of peripheral blood or bone marrow.

2.3. Statistical considerations

We anticipated a sample size of between 80 and 100 patients. To explore differences between our study and the response rates of patients in clinical trials, we performed a meta-analysis of the previous phase I–II studies and single RCT addressing response rates (Table 1) in previously treated patients with relapsed or refractory AML or MDS, recognizing that these trials had differing eligibility criteria and other protocol characteristics. Of note, the CLASSIC II study was excluded from this meta-analysis as that trial evaluated clofarabine in previously untreated patients with AML who were considered to have a low likelihood of favorable outcome with intensive induction therapy [17]. We then applied confidence intervals (CI) surrounding the ORR and CRR of the previous studies and our data using the modified Wald method and GraphPad software [18]. These calculations produced a 95% CI of .41–.51 (41–51%) with regard to overall response rate in the meta-analysis. Data including means, medians, and simple proportions of specific patient subsets are reported using descriptive statistics.

3. Results

3.1. Baseline characteristics

A total of 112 patients treated with clofarabine at DFCI/BWH were identified. Of these, 28 were excluded from subsequent analysis: 19 because they had ALL, 7 were given clofarabine exclusively as part of a conditioning regimen prior to allogeneic stem cell transplantation, 1 proved to be a medical record test patient, and 1 did not have any follow-up to assess response (Fig. 1). There were 65 patients who received clofarabine and cytarabine combination therapy and 19 who received clofarabine monotherapy. Of these patients, 81 had a diagnosis of relapsed or primary refractory AML and 3 had MDS that had not responded to hypomethylating agents.

Baseline characteristics of all patients studied included a median age of 51 years; the clofarabine monotherapy group had an older median age of 72 years (Table 2). Performance status was 0 in 18%, 1 in 35%, and 2 or greater for 15%, while 32% were "unknown" (as PS was documented only if a clinical note just prior to therapy contained this information). Cytogenetic risk assignment for the AML patients was based on the Medical Research Council (MRC) classification [19]; Sixty-five percent had an intermediate risk cytogenetic profile. About two thirds of patients had relapsed disease and just under one third were primary refractory.

3.2. Dosing

Almost all patients (n = 62) receiving combination therapy were administered cytarabine at 1 g/m^2/day on days 1–5 and