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Phase II trial of clofarabine and daunorubicin as induction therapy for acute myeloid leukemia patients greater than or equal to 60 years of age

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ABSTRACT

We designed a phase II study evaluating the upfront combination of clofarabine and daunorubicin in acute myeloid leukemia (AML) patients ≥ 60 years old. The median age of the 21 patients was 69 (range 60–85) years. Fourteen patients (67%) had unfavorable risk features. The principal toxicities were grade ≥3 infections and prolonged myelosuppression. Three (14%) deaths occurred from infectious complications. Six (28.6%) patients achieved complete remission including three (21.4%) of 14 patients with unfavorable AML. The median disease-free survival was 6.8 months and the median overall survival was 11.2 months.

1. Introduction

The outcome of acute myeloid leukemia (AML) in patients ≥60 years old remains poor with a median survival of approximately 12 months. This poor outcome is partially explained by the inability of patients to tolerate treatment and by the aggregation of unfavorable risk factors including secondary leukemia, adverse karyotypes, aberrant signaling pathways such as FLT3-internal tandem duplication (ITD), and overexpression of P-glycoprotein [1].

Clofarabine, a second generation purine nucleoside analog, was designed to overcome some of the above features. Specifically, halogenation at the 2 position of adenine and substitution of a fluorine group at the C-2 position of the arabino furanosyl moiety allows high affinity for deoxycytidine kinase, prolonged intracellular retention of clofarabine triphosphate, potent inhibition of DNA synthesis and ribonucleotide reductase, and resistance to P-glycoprotein [2]. In addition, clofarabine is active in non-dividing cells as well as cells with a low proliferation rate, enhancing potential activity against leukemic stem cells. Clofarabine is approved for pediatric relapsed/refractory acute lymphoblastic leukemia [3] but there has been significant interest in its role in AML. In particular, the combination of clofarabine and cytarabine has shown promising activity as induction therapy in newly diagnosed AML patients 50 years of age or older [4]. Since daunorubicin is also active in AML [5], we conducted a phase II study of clofarabine plus daunorubicin in newly diagnosed AML patients older than 60 years of age. The primary end point of the study was treatment response, and the secondary end points were disease-free survival (DFS) and overall survival (OS).

2. Patients and methods

2.1. Patient criteria

Newly diagnosed AML patients ≥ 60 years of age were eligible to participate in the study following pathological disease confirmation. Patients with acute promyelocytic leukemia with *t*(15;17) or other variants were excluded. Additional inclusion criteria were no previous therapy for AML with the exception of hydroxyurea, Eastern Cooperative Oncology Group performance status ≤ 2,

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left ventricular ejection fraction ≥ 45%, as well as adequate renal (defined as an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2 per modified diet in renal disease equation) and hepatic (serum bilirubin ≤ 1.5 × the upper limit of normal; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤ 2.5 × the upper limit of normal) functions. Major exclusion criteria included active clinical infection, including HIV positivity, and clinical evidence of central nervous system disease. Patients with a diagnosis of previous malignancy were also excluded unless they had been free of documented disease for a minimum of three years. Patients had to be without evidence of severe concurrent disease or organ dysfunction involving the heart, kidney or liver that would place the patient at undue risk from induction chemotherapy. Approval of the study was granted by the Scientific Review Committee and the Institutional Review Board of Roswell Park Cancer Institute. All patients signed informed consent prior to study initiation. The study was conducted in accordance with the basic principles of the Declaration of Helsinki. The study was registered as NCT00814164.

Karyotype analyses were performed at Roswell Park Cancer Institute. We used the European LeukemiaNet classification [6]. *FLT3*-ITD [7], *NPM1* [8] and *CEPBA* [9] mutations were assessed at Roswell Park Cancer Institute.

2.2. Treatment plan

The study design consisted of three treatment cycles (one induction and up to two cycles of consolidation) unless the patient exhibited evidence of treatment failure, disease recurrence, or an unacceptable toxicity that led to treatment discontinuation. During induction, clofarabine was administered at 20 mg/m^2 as a 1 h intravenous (IV) infusion for five days followed 3 h later (from the end of infusion) by daunorubicin 50 mg/m^2 administered as IV infusion (over 5 min) given every other day for three doses (days 1, 3 and 5). Patients who achieved remission after induction were offered up to two cycles of consolidation therapy with clofarabine administered at 20 mg/m^2 as a 1 h IV infusion for three consecutive days followed 3 h later (from the end of infusion) by daunorubicin 50 mg/m^2 administered as IV infusion (over 5 min) given every other day for two doses (days 1 and 3). Prophylactic antibacterial, anti-fungal and anti-viral agents were utilized according to institutional guidelines.

2.3. Response criteria

Treatment response was assessed using the International Working Group criteria [10]. Complete response (CR) was defined as recovery of normal hematopoiesis with an absolute neutrophil count ≥ 1.0 × 10^9/L and a platelet count ≥ 100 × 10^9/L and normalization of the bone marrow blasts (<5%). CR without platelet recovery was defined as CRp. If assessment of bone marrow examination following induction confirmed >5% blasts, then a second treatment cycle could be administered as re-induction but not before Cycle 1 Day 28. If the marrow assessment following induction precluded a definitive treatment decision (e.g., a hypocellular or regenerating marrow), then a repeat bone marrow examination was performed every 7–14 days through day 84 until a determination could be made. If a definitive treatment decision could not be made by day 84, then the patient was assessed as a treatment failure. If the patient met the criteria for leukemic progression, then the patient was considered a treatment failure and no further treatment cycles were administered.

2.4. Statistical analysis

This was a phase II study in adult AML patients aged ≥ 60 years old. The study was planned to enroll 60 patients with an interim analysis after 30 patients. The study was prematurely halted by the sponsor due to the unfavorable outcome. Fisher's exact test was used to study the association between categorical variables. The Wilcoxon rank sum test was used to compare the response groups in regards to numeric variables. The logistic regression model was used to test the difference between response and no-response groups for multivariate analysis. The estimated DFS and OS distributions were obtained using the Kaplan–Meier method. Using this distributional estimate, summary descriptive statistics such as the median survival and a 95% confidence interval (CI) of the median survival were obtained. Exact 95% CI using the Clopper–Pearson method was used to evaluate response rate. A 0.05 nominal significance level was used in all testing. All statistical analyses were done using SAS (version 9.3).

2.5. End point definitions

Overall response (OR) was defined as the sum of the number of patients with morphologic CR plus those with CRp divided by the total number of patients. Duration of remission was defined as the time from first objective documentation of CR or CRp to date of first objective documentation of disease relapse, initiation of alternative anti-leukemic therapy while in remission (including stem cell transplantation), or death due to any cause, whichever occurred first. Patients who did not respond (i.e., those who failed to achieve CR or CRp) were coded as failures at the last date on which their disease status was assessed. DFS was defined as the time from first objective documentation of CR or CRp until the date of first objective documentation of disease relapse or death due to any cause, whichever occurred first. OS was defined as the time from date of treatment initiation until date of death due to any cause.

Table 1
Patient characteristics.

Characteristics	Number	%
Age		
Median	68	
Range	60–85	
ELN classification		
Favorable	3	14
Intermediate-I	5	24
Intermediate-II	4	19
Adverse[a]	9	43
Molecular aberrations		
FLT3-ITD	1	5
NPM1	4	19
CEBPA	1	5
White blood cell count (×109/L)		
Median	7.89	
Range	0.22–134.0	
Secondary AML		
Antecedent hematologic disorder	10	48
Previous treatment for another malignancy	0	0
ECOG performance status		
0	1	5
1	16	76
2	4	19

Abbreviations: AML, acute myeloid leukemia; *CEBPA*, CAAT/enhancer-binding protein alpha; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; *FLT3*-ITD, Fms-like tyrosine kinase 3-internal tandem duplication; *NPM1*, nucleophosmin 1.

[a] This cohort included one patient with both del(5) and del(7), three patients with del(5)/−5, and four patients with del(7)/−7. Six patients had complex karyotype.

3. Results

3.1. Patient characteristics

Between December 2008 and June 2011, 21 patients were enrolled. The median age was 69 (range 60–85) years, and 12 (57%) were women. Nine patients (43%) were older than 70 years of age. Fourteen patients (67%) had unfavorable risk features consisting of secondary AML (all had antecedent hematologic disorders, none had therapy-related AML), presence of complex karyotype (≥3 aberrations) and/or the presence of *FLT3*-ITD (Table 1). All 21 patients completed one induction cycle, one patient received a second induction cycle due to residual disease, and six (29%) patients received at least one consolidation regimen.

3.2. Response

Among the 21 patients, eight achieved a CR/CRp to induction therapy (six CR, two CRp) for an OR rate of 38.1% (95% CI, 18.1–61.6%) and CR rate of 28.6% (95% CI, 11.3–52.2%) (Table 2). In multivariate analyses, the unfavorable group (defined as secondary AML, complex karyotype, and *FLT3*-ITD) showed significant association with response when controlling for age, white blood cell count, and performance status ($P = 0.0311$); however, no

Table 2
Response characteristics.

	Response (%)	Unfavorable AML (%)	Age ≥ 70	*N*
CR	6 (28.6)	3 (21.4)	3 (33)	6
CRp	2 (9.5)	0 (0)	2 (22)	2
NR	13 (61.9)	11 (78.6)	4 (44)	13
Total	21 (100)	14 (100)	9 (100)	21

Abbreviations: AML, acute myeloid leukemia; CR, complete response; CRp, CR without platelet recovery; *N*, number; NR, no response.