

# Comparison of Clofarabine-Based Regimens Versus Etoposide Plus Mitoxantrone as Salvage Chemotherapy for Patients with Relapsed or Refractory Acute Myeloid Leukemia

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## Abstract

**Introduction:** There is insufficient evidence regarding the optimal chemotherapy regimen for treatment of relapsed or refractory acute myeloid leukemia (RR-AML). We retrospectively compared the outcomes and toxicities between salvage chemotherapy with etoposide plus mitoxantrone (EM) versus clofarabine-based regimens in patients with RR-AML.

**Materials and Methods:** Consecutive patients with RR-AML who received  $\geq 1$  cycle of EM or a clofarabine-based regimen between March 2003 and April 2017.

**Results:** A total of 93 patients were included in the study. Sixty-nine patients received EM and 24 patients received clofarabine-based regimens. Baseline characteristics were matched, except for a higher rate of previous EM therapy and primary refractory disease in the clofarabine arm. The overall remission rate (complete remission plus complete remission with incomplete hematologic recovery) was 36.2% in the EM arm versus 29.2% in the clofarabine arm ( $p = 0.62$ ). The 3-year event-free survival (EFS) and overall survival (OS) was 17.6% and 41% in the EM arm, compared to 4.6% ( $p = 0.18$ ) and 5% ( $p < 0.001$ ) in the clofarabine arm. Of those treated with EM, 36.2% could undergo subsequent allogeneic hematopoietic cell transplantation (allo-HCT) versus 12.5% of those in the clofarabine arm ( $p = 0.04$ ). Grade 3 or higher non-hematologic toxicities occurred in 35 (50.7%) patients in the EM arm, compared to 18 (75%) patients with a clofarabine-based regimen ( $p = 0.04$ ). This is the first comparison of these two salvage chemotherapy options. Unfortunately, the imbalance with more refractory and heavily pretreated patients in the clofarabine arm limits conclusions, and more studies are necessary to validate outcomes with these regimens.

**Keywords:** Hematologic malignancy, transplantation, outcomes, remission, treatment

## INTRODUCTION

Although 60–80% of patients with acute myeloid leukemia (AML) will attain an initial remission, even with appropriate post-induction therapy >50% will eventually relapse.<sup>1-3</sup> Those with relapsed or refractory acute myeloid leukemia (RR-AML) require

further chemotherapy with a goal of achieving remission as a bridge to allogeneic hematopoietic cell transplantation (allo-HCT). Allo-HCT remains the only curative option in these patients and shows significant survival advantage over other treatment strategies.<sup>4</sup> Potent graft-versus-leukemia effects seen with allo-

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HCT result in durable remissions and improved relapse-free survival (RFS).<sup>5,6</sup> However, the remission status at the time of allo-HCT is a significant predictor of post-transplantation outcomes and achieving deeper remissions prior to allo-HCT is of paramount importance.<sup>7-11</sup> Unfortunately, no consensus exists regarding the optimal salvage chemotherapy regimen in this setting and the choice of regimen is largely dependent on institutional practice.

Etoposide plus mitoxantrone (EM) has been reported in several studies with overall remission rates (ORR) [complete remission (CR) plus complete remission with incomplete hematologic recovery (CRi)] of 16–61%.<sup>12-18</sup> Clofarabine, either as monotherapy or in combination therapy, results in ORR rates of 21–61%.<sup>19-26</sup> However, no comparative data exist comparing salvage chemotherapy in RR-AML patients with EM versus clofarabine-based regimens. We report a retrospective analysis comparing EM versus clofarabine-based regimens to offer insights into the optimal management of RR-AML.

### MATERIALS AND METHODS

#### Patient Population

Consecutive patients with RR-AML who were admitted to the inpatient Hematologic Malignancy Service at West Virginia University between March 2003 and April 2017 receiving either etoposide (100 mg/m<sup>2</sup> IV daily x 5 doses) plus mitoxantrone (10 mg/m<sup>2</sup> IV daily x 5 doses) or a clofarabine-based regimen were included. Patients in the clofarabine arm received one of the following regimens: clofarabine (20-40 mg/m<sup>2</sup> IV daily x 5 doses) plus cytarabine (1-2 g/m<sup>2</sup> IV daily x 5 doses), clofarabine (25-40 mg/m<sup>2</sup> IV daily x 4-5 doses) plus cyclophosphamide (340-440 mg/m<sup>2</sup> IV daily x 4-5 doses) plus or minus etoposide (100 mg/m<sup>2</sup> IV daily x 4-5 doses), or clofarabine monotherapy (20 mg/m<sup>2</sup> IV daily x 5 doses). Patients with acute promyelocytic leukemia were excluded. The study was approved by the Institutional Review Board at West Virginia University.

#### Endpoints and Study Definitions

The primary study outcome was comparison of ORR between patients receiving EM versus clofarabine-based regimens. Secondary endpoints included comparison of median overall survival (OS), event-free survival (EFS), RFS, toxicities, and ability to undergo subsequent allo-HCT.

Patients were stratified into favorable, intermediate, and adverse risk groups according to genetic abnormalities as described in the European Leukemia Net (ELN) recommendations.<sup>27</sup> ORR included patients either achieving a CR or a CRi. CR was defined as less than 5% blasts in the bone marrow, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease, and peripheral blood count recovery with a neutrophil count of at least 1.0 x 10<sup>9</sup>/L and platelet count of at least 100 x 10<sup>9</sup>/L.<sup>27</sup> CRi was defined as meeting all criteria for CR, except for residual neutropenia (neutrophil count less than 1.0 x 10<sup>9</sup>/L) or thrombocytopenia (platelet count less than 100 x 10<sup>9</sup>/L).<sup>27</sup> OS was measured from the date of chemotherapy initiation to the date of death or last follow-up. EFS was measured from the date of chemotherapy initiation to the date of treatment failure, relapse, death, or last follow-up. Treatment failure was defined as failure to achieve remission after chemotherapy initiation. RFS was only reported for patients achieving CR or CRi and was measured from the date of CR or CRi to the date of relapse or death.<sup>27</sup> Primary refractory disease was defined as failure to attain CR or CRi after two or more courses of induction chemotherapy.<sup>27</sup>

National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, was used to grade adverse events.<sup>28</sup> Neutrophil recovery was defined as the first of three consecutive days to an absolute neutrophil count (ANC) of > 0.5 x 10<sup>9</sup>/L, post-nadir. Platelet recovery was defined as the first of seven consecutive days to platelet count above 20 x 10<sup>9</sup>/L, without platelet transfusion.

#### Statistical Methods

Descriptive statistics were used to summarize baseline patient characteristics. Categorical data were described using contingency tables. Continuous variables were summarized using median with range. Fisher's exact test and Wilcoxon rank test were used to assess the categorical variables and continuous variables, respectively. The Kaplan-Meier method was used to estimate the survival distributions, which were then compared using the log-rank test. Multivariable data analyses with various risk factors and baseline patient characteristics were conducted using Cox proportional hazards regression for time-to-event outcomes such as OS, EFS, and RFS. For patients who were alive at the time of analysis, follow-up was censored as of the date of last contact. Statistical inferences were

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based on two-sided tests at a significance level of  $p < 0.05$ . Statistical analyses were performed using SAS v9.1 (SAS Institute, Cary, NC) software and statistical software R v3.31 (R Foundation, Vienna, Austria).

### RESULTS

#### Patient Characteristics

Ninety-three patients were identified who met the inclusion criteria. Sixty-nine patients received EM and 24 patients received a clofarabine-based regimen. Baseline characteristics were similar between treatment groups (Table 1), except significantly more patients in the clofarabine arm had primary

refractory disease compared to EM (45.8% vs. 15.9%,  $p = 0.005$ ). Patients receiving a clofarabine-based regimen were more likely to have received prior EM therapy (75%,  $n=18$ ). No patients in the EM arm received prior clofarabine. In addition, more patients in the EM arm underwent prior allo-HCT, although it was not statistically significant (24.6% vs. 12.5% in clofarabine arm,  $p = 0.26$ ). Clofarabine was given as a single agent in 1 (4.2%) patient, in combination with cytarabine in 17 (70.8%) patients, combined with cyclophosphamide in 3 (12.5%) patients, and with cyclophosphamide and etoposide in 3 (12.5%) patients.

**Table 1.** Patient Demographics and Baseline Characteristics

	<b>Etoposide + Mitoxantrone (n=69)</b>	<b>Clofarabine-based Regimen (n=24)</b>	<b>P-value</b>
<b>Median age, years (range)</b>	50 (18-75)	48.5 (19-68)	0.92
<b>Male gender</b>	33 (47.8%)	16 (66.7%)	0.15
<b>Ethnicity</b>			
Caucasian	63 (91.3%)	20 (83.3%)	0.43
African-American	5 (7.2%)	4 (16.7%)	
Other	1 (1.4%)	0 (0%)	
<b>Median BMI, kg/m<sup>2</sup> (range)</b>	29.7 (16.5-58.7)	25.9 (19.6-53.6)	0.45
<b>ECOG performance status</b>			
0	16 (23.2%)	1 (4.2%)	0.098 (0/1 vs 2/3)
1	32 (46.4%)	14 (58.3%)	
2	6 (8.7%)	5 (20.8%)	
3	1 (1.4%)	2 (8.3%)	
Unknown	14 (20.3%)	2 (8.3%)	
<b>Median WBC at start of therapy, <math>\times 10^3</math> (range)</b>	5.7 (0.2-102)	5.7 (0-72.8)	0.56
<b>Primary refractory disease</b>	11 (15.9%)	11 (45.8%)	0.005
<b>Prior MDS</b>	11 (15.9%)	4 (16.7%)	0.99
<b>Treatment-related AML</b>	4 (5.8%)	2 (8.3%)	0.64
<b>Median lines of prior chemotherapy (range)</b>	2 (1-7)	3 (2-6)	0.063
<b>Prior therapy</b>			
Cytarabine/Anthracycline (7+3)	68 (98.6%)	23 (95.8%)	<0.001
High-dose Cytarabine containing regimen	61 (88.4%)	19 (79.2%)	
Hypomethylating agent	5 (7.3%)	4 (16.7%)	
Etoposide-Mitoxantrone	NA	18 (75%)	
<b>Prior allogeneic HCT</b>	17 (24.6%)	3 (12.5%)	0.26
<b>ELN risk category</b>			
Favorable	13 (18.8%)	3 (12.5%)	0.74
Intermediate	26 (37.7%)	11 (45.8%)	
Adverse	30 (43.5%)	10 (41.7%)	

Abbreviations: BMI – body mass index, ECOG – Eastern Cooperative Oncology Group, WBC – white blood cell count, MDS – myelodysplastic syndrome, AML – acute myeloid leukemia, HCT – hematopoietic cell transplant, ELN – European Leukemia Net

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### Responses

The ORR for patients who received EM was 36.2% (CR=24.6% and CRi=11.6%), compared to 29.2% (CR=20.8% and CRi=8.3%) in the clofarabine arm,  $p = 0.62$ . The ORR for the 6 EM-naïve patients in the clofarabine arm was 33.3% and none underwent subsequent allo-HCT. Twenty-five (36.2%) patients in the EM arm underwent subsequent allo-HCT, compared to only 3 (12.5%) patients in the clofarabine arm ( $p = 0.04$ ). Among the patients who underwent prior allo-HCT, 2 (11.8%) patients in the EM arm and no patients in the clofarabine arm underwent subsequent allo-HCT,  $p = 1.00$ .

### Survival

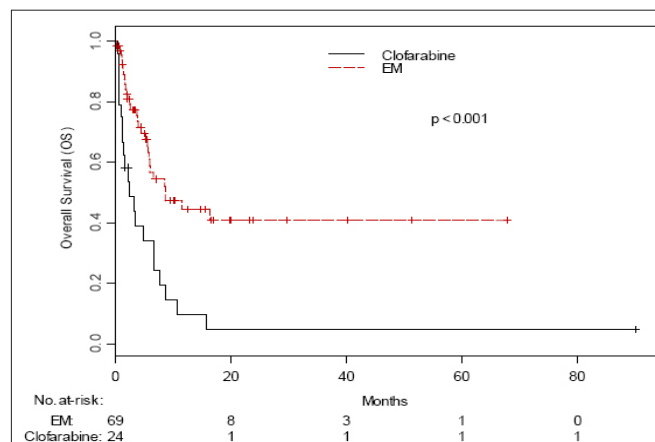
The median OS for patients treated with EM was 8.7 months [95% confidence interval (CI): 5.9 to 80

months], compared to 2.4 months (95% CI: 1.5 to 7.7,  $p < 0.001$ ) for those treated with a clofarabine-based regimen. The 3-year OS was 41% in the EM arm and 5% in the clofarabine arm [hazard ratio (HR): 0.34; 95% CI: 0.20 to 0.60;  $p < 0.001$ ; Figure 1A]. The 3-year EFS was 17.6% in the EM arm and 4.6% in the clofarabine arm [HR: 1.41; 95% CI: 0.85 to 2.33;  $p = 0.18$ ; Figure 1B]. Among the patients achieving CR or CRi, the 3-year RFS was 45.5% in the EM arm and 12.5% in the clofarabine arm [HR: 0.44; 95% CI: 0.17 to 1.12;  $p = 0.077$ ; Figure 1C]. Multivariable Cox regression analyses showed that worse OS was significantly associated with receiving a clofarabine-based regimen (HR: 2.17), male gender (HR: 2.37), receiving a greater number of prior therapies (HR: 1.75), and having an adverse ELN risk category (HR: 2.10; Table 2).

**Table 2. Multivariable Cox Regression Analysis for Overall Survival**

Variable	Hazard Ratio	P-value
Etoposide + Mitoxantrone	0.46	0.016
Male	2.37	0.014
Age	1.02	0.19
Caucasian	1.23	0.59
BMI	0.99	0.68
ECOG > 0	1.73	0.22
History of MDS/MPD	1.56	0.35
Prior therapy	1.75	0.001
Prior HCT	0.65	0.33
Adverse ELN risk	2.10	0.031

Abbreviations: BMI – body mass index, ECOG – Eastern Cooperative Oncology Group, MDS – myelodysplastic syndrome, MPD – myeloproliferative disease, HCT – hematopoietic cell transplantation, ELN – European Leukemia Net



**Figure 1A**

## Comparison of Clofarabine-Based Regimens Versus Etoposide Plus Mitoxantrone as Salvage Chemo therapy for Patients with Relapsed or Refractory Acute Myeloid Leukemia

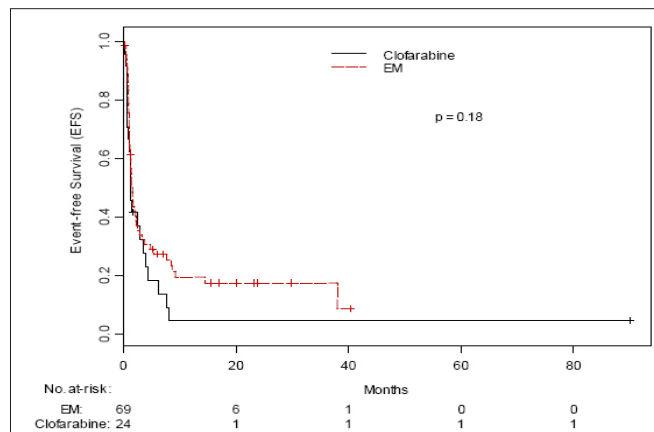


Figure 1B

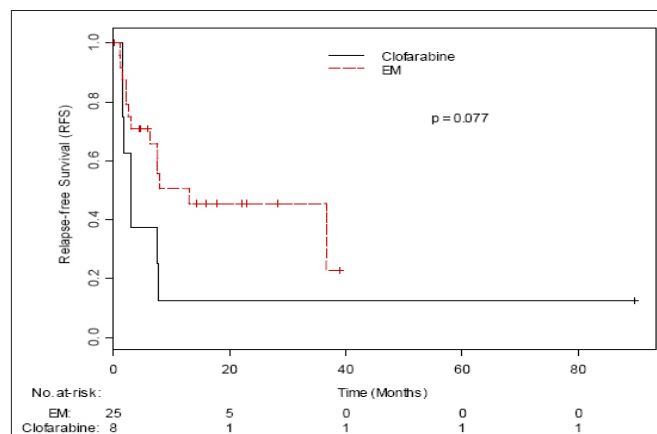


Figure 1C

Figure 1. Kaplan-Meier curves for (A) OS, (B) EFS, and (C) RFS

### Toxicity

Thirty-five (50.7%) patients treated with EM developed a grade 3 or higher non-hematologic toxicity, compared to 18 (75%) of those treated with a clofarabine-based regimen ( $p = 0.04$ ). The full details of specific non-hematologic toxicities are listed in Table 3. Seventeen (24.6%) patients in the EM arm experienced treatment-related mortality

within 60 days, compared to 11 (45.8%) patients in the clofarabine arm ( $p = 0.07$ ). The median time to neutrophil recovery for the EM arm was 28 days (range: 14 to 751 days) and 24 days (range: 15 to 98 days) for the clofarabine arm,  $p = 0.96$ . The median time to platelet recovery for the EM arm was 26 days (range 14 to 85 days) and 34 days (range 20 to 111 days) for the clofarabine arm,  $p = 0.32$ .

Table 3. Grade 3 to 4 Non-Hematological Adverse Events

	Etoposide + Mitoxantrone (n=69)	Clofarabine-based Regimen (n=24)	P-value
<b>Hepatotoxicity</b>	2 (2.9%)	6 (25%)	0.003
<b>Nephrotoxicity</b>	0 (0%)	3 (12.5%)	0.016
<b>Infection</b>			
Bacteremia	18 (26.1%)	9 (37.5%)	0.31
Pneumonia	7 (10.1%)	2 (8.3%)	0.99
Sepsis	3 (4.3%)	4 (16.7%)	0.07
Urinary tract infection	4 (5.8%)	0 (0%)	0.57
Cellulitis	3 (4.3%)	1 (4.2%)	0.99
Neutropenic enterocolitis	3 (4.3%)	2 (8.3%)	0.60



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### DISCUSSION

To our knowledge, there have been no previous published studies comparing outcomes and toxicities between EM and clofarabine-based regimens for the treatment of RR-AML. With an ORR of 36.2% for EM and 29.2% for clofarabine-based regimens, these remission rates are in line with previous reports.<sup>12-26</sup> Patients treated with EM had significantly longer OS and greater ability to undergo subsequent allo-HCT. Significantly more patients in the clofarabine arm developed a grade 3 or higher non-hematologic toxicity.

Although remission rates appeared to be similar, significantly more patients in the EM arm could undergo allo-HCT. This may be due to several reasons. Patients in the clofarabine arm were more heavily pretreated and had a significantly greater rate of primary refractory disease. In addition, many patients in this arm previously received EM making it difficult to make strong conclusions when comparing the two arms. Although RFS did not reach statistical significance, it appeared that patients in the clofarabine arm achieving remission did not maintain this remission for as long as the EM patients. Many of them may have relapsed before transplantation could be accomplished. It is also possible that due to higher rates of toxicities (renal/liver), patients were no longer candidates for transplantation. The improvement in OS with EM was likely impacted by more of these patients undergoing allo-HCT. For the 6 patients in the clofarabine arm who were EM-naïve, 33.3% achieved remission, with a median OS and median EFS of 2.8 months and 1.0 month, respectively. None of these patients were able to subsequently undergo allo-HCT. These outcomes do not appear different than the clofarabine patients who had previously received EM.

A multivariable data analysis identified patients receiving EM, being of female gender, receiving a fewer number of prior therapies, and not having an adverse ELN risk category as being significantly more likely to have a prolonged OS. Many patients in the EM arm received a fewer number of prior therapies indicating a relatively less heavily pretreated and potentially less resistant disease compared to those in the clofarabine arm. Adverse ELN risk category indicates leukemia that is more resistant to chemotherapy, so those patients without this risk category are expected to

have better outcomes. Additionally, those treated with EM developed significantly less hepatotoxicity and nephrotoxicity compared to those in the clofarabine arm.

### CONCLUSION

We found EM to have improved OS, increased ability to undergo allo-HCT, and decreased toxicity than clofarabine-based regimens. However, it is difficult to make strong conclusions due to the imbalance in prior therapies. This is the first comparison of these two salvage chemotherapy regimens and further study is necessary.

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