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Scientific Letter

A Real-World Study on Clofarabine and Cytarabine Combination in Patients with Relapsed/Refractory Acute Myeloid Leukemia

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Long-term survival has increased in patients with acute myeloid leukemia (AML) over the last two decades due to improved supportive care and improved access to allogeneic transplantation than to substantial improvement of chemotherapy effectiveness. In particular, patients with relapsed/refractory (R/R) AML, who usually have an unfavorable prognosis, should undergo allogeneic transplantation after a second complete remission (CR2) to potentially achieve a treatment success.[1] Unfortunately, only a few R/R AML patients can be treated with intensive therapy and the probability of remission after salvage is significantly lower than after induction therapy. However, the CR rate is 55% in patients aged between 16 and 49 years and even lower (20-30%) in older cohorts. Additionally, only 66% of patients aged 16-49 years who achieve CR are eligible to allogeneic transplantation with a 5-year overall survival (OS) of 40%. The transplantation rate is even lower in older patients, and worst outcomes (3-year OS: ~10%) can be associated not only with increasing age and comorbidities but also with unfavorable cytogenetic and molecular profiles. Factors associated with poor prognosis are short CR1 duration, older age at the time of relapse, unfavorable cytogenetics at diagnosis and relapse after allogeneic transplantation. It is worth noting that mortality rate remains high among patients who undergo allogeneic transplantation in CR2, due to high transplant-related mortality (TRM) and relapse rate. The outcome of patients who relapse after allogeneic transplantation is particularly poor and the earlier is the relapse, the worse is the outcome. In this context, other factors associated with poor outcome are age >40 years, active graft versus host disease (GvHD), unfavorable cytogenetics at diagnosis, matched unrelated donor (MUD) or cord blood donor.[2-4]

Given the lack of a standardized strategy for R/R AML and its disappointing prognosis, the enrollment in clinical trials is still considered the best option. Nonetheless, only a minority of patients can be recruited based on restrictive selection criteria and the enrollment of specialized centers. Chemotherapy-based salvage regimens are usually prescribed to patients with R/R AML. Most of the protocols include the combination of high doses of Cytarabine with other agents, such as anthracyclines, Etoposide, and nucleoside analogs. The most frequently administered combinations are Fludarabine, Cytarabine and Idarubicine (FLAI) or Mitoxantrone, Etoposide and Cytarabine (MEC). Recently, a systematic literature review showed a relatively high CR rate (44-60%), a short CR duration (5-10 months) and OS (6-9 months) in individuals exposed to standard chemotherapy protocols.[1]

The efficacy of the nucleoside analog Clofarabine has been assessed in patients with AML both in monotherapy and in combination, specifically with Cytarabine based on their synergistic action.[5] In particular, administration of Clofarabine with high doses of Cytarabine (CLARA) showed a CR rate of 44% and a mean OS of 6 months in R/R AML patients, together with a favorable safety profile.[6] In case of prescription of CLARA as a bridge to allogeneic transplantation, a median OS of 24 months and a 3-year OS of 55% can be achieved. Furthermore, CR can also be obtained in patients who were non-responders to Fludarabine-containing regimens.[7-8]

We retrospectively evaluated 47 and 22 patients with R/R AML consecutively exposed between 2001 and 2017 to second- and third-line therapy, respectively, in the Hematology units of the University Hospitals of Sassari and Cagliari. The aim of this observational study was to compare effectiveness, i.e., overall response rate (ORR), OS and relapse-free survival (RFS), and safety profile of CLARA and other standard chemotherapy protocols. In the cohort exposed to second-line therapy, 15 received CLARA and 32 different chemotherapy regimens (control

group), whereas 7/22 and 15/22 were treated with CLARA or with other regimens in the cohort of the third-line therapy, respectively. No specific criteria were applied to select either CLARA or different therapeutic regimens, but all cases were discussed collegially taking into consideration previous lines of therapy and expected toxicities. All therapeutic approaches were allied with a primary intention to carry on with transplant after reaching CR. Dosages of Clofarabine in the CLARA regimen ranged from 22.5 to 40 mg/m^2, followed 4 hours later by a dose of Cytarabine from 1 to 2 g/m^2 for 5 days. The most frequently prescribed chemotherapy schemes in the control group were: Fludarabine-Cytarabine-based regimens with or without anthracycline (21 and 1 patients on second- and third-line therapy, respectively) and Cytarabine-anthracycline-Etoposide-based combinations (10 and 6 patients on second- and third-line therapy, respectively). Other less frequently administered regimens were based on Gemtuzumab ozogamicin, with or without chemotherapy (5 cases on third-line treatment). Comparisons between the groups mentioned above were carried out with chi-squared or Fisher's exact tests for qualitative variables and Student's t-test distribution or Mann-Whitney's tests for parametric and nonparametric variables. All analyses were performed with the statistical software Stata version 15 (StatsCorp, Texas).

As shown in **tables 1** and **2**, the median (IQR) age of the entire cohort was 53 (33-64) years. According to the 2016 World Health Organization (WHO) classification, among patients treated in second line 25 patients (53%) had not otherwise specified AML (AML-NOS), 15 (32%) AML with myelodysplasia-related changes, 3 (6%) therapy-related AML, 2 (4%) AML with t(8;21) and 2 (4%) AML with NPM1 mutation. Among patients treated in third line 10 patients (45%) had AML-NOS, 8 (36%) AML with myelodysplasia-related changes, 1 (5%) therapy-related AML, 1 (5%) AML with t(8;21) and 2 (9%) AML with NPM1 mutation. According to the 2017 prognostic stratification by European Leukemia Net (ELN) 8 (12%), 38 (55%), and 23 (33%) patients were classified as at low, intermediate, and high-risk, respectively. Thirty-two (46%) had relapsed AML, whereas 37 (54%) had a primary refractory disease. No statistically significant differences were found between CLARA and control group according to age, WHO subtypes, ELN classification, and disease status in patients treated in both second and third line. We specifically evaluated the potential impact of latency between remission and relapse in each group, but no significant differences could be detected. In fact, in patients treated in second line median (IQR) lag between remission and relapse was 2 and 0 months in CLARA and control group (p-value: 0.60), respectively while in

Table 1. Characteristics and outcomes of patients treated in second line

Variables		Control group (n= 32)	CLARA 2^ line (n= 15)	p-value
Median (IQR) age at diagnosis, years		53.5 (46.5-64.0)	60 (45-64)	0.89
WHO, n (%)	AML with t(8;21)	1 (3.1)	1 (6.7)	0.37
	AML with mutated NPM1	1 (3.1)	1 (6.7)	
	AML with MDS-related changes	12 (37.5)	3 (20.0)	
	AML therapy-related	1 (3.1)	2 (13.3)	
	AML NOS	17 (53.1)	8 (53.3)	
ELN category risk, n (%)	Favourable	2 (6.3)	2 (13.3)	0.57
	Intermediate	20 (62.5)	7 (46.7)	
	High	10 (31.3)	6 (40.0)	
Disease status, n (%)	Primary refractory	20 (62.5)	6 (40.0)	0.15
	Relapsed	12 (37.5)	9 (60.0)	
Response, n (%)	CR	9 (28.1)	8 (53.3)	0.29
	CRi	1 (3.1)	1 (6.7)	
	PR	4 (12.5)	1 (6.7)	
	RD	17 (53.1)	4 (26.7)	
	Death in aplasia	1 (3.1)	1 (6.7)	
Receiving stem cell transplant, n (%)		2 (6.3)	3 (20.0)	0.31
Median (IQR) OS, months		7.5 (3-17)	8 (2-16	0.98
Median (IQR) RFS, months		0 (0.0-2.5)	3 (0-8)	0.02
Infections, n (%)		17 (53.1)	9 (60.0)	0.66
Pneumonia, n (%)		10 (31.3)	5 (33.3)	0.88
Bacteraemia and sepsis, n (%)		10 (31.3)	7 (46.7)	0.31
Hepatic toxicity, n (%)		3 (9.4)	5 (33.3)	0.09

Abbreviations: CLARA (Clofarabine+Cytarabine); CR (complete response); CRi (complete response with incomplete recovery); ELN (Eurpean Leukemia Net); IQR (interquartile range); OS (overall survival); PR (partial response); RD (refractory disease); RFS (relapsed free survival); SCT (stem cell transplantation).

Table 2. Characteristics and outcomes of patients treated in third line

Variables		Control group (n= 15)	CLARA 3^ line (n= 7)	p-value
Median (IQR) age at diagnosis, years		53 (33-62)	53 (45-60)	0.94
WHO, n (%)	AML with t(8;21)	1 (6.7)	0 (0.0)	0.35
	AML with mutated NPM1	0 (0.0)	2 (28.6)	
	AML with MDS-related changes	6 (40.0)	2 (28.6)	
	AML therapy-related	1 (6.7)	0 (0.0)	
	AML NOS	7 (46.7)	3 (42.9)	
ELN category risk, n (%)	Favourable	2 (13.3)	2 (28.6)	0.42
	Intermediate	9 (60.0)	2 (28.6)	
	High	4 (26.7)	3 (42.9)	
Disease status, n (%)	Primary refractory	7 (46.7)	4 (57.1)	1.0
	Relapsed	8 (53.3)	3 (42.9)	
Response, n (%)	CR	2 (13.3)	2 (28.6)	0.64
	CRi	-	-	
	PR	1 (6.7)	0 (0.0)	
	RD	11 (73.3)	4 (57.1)	
	Death in aplasia	1 (6.7)	1 (14.3)	
Receiving stem cell transplant, n (%)		3 (20.0)	2 (28.6)	1.0
Median (IQR) OS, months		3 (2-10)	2 (2-6)	0.52
Median (IQR) RFS, months		0 (0-0)	0 (0-3)	0.17
Infections, n (%)		5 (33.3)	5 (71.4)	0.17
Pneumonia, n (%)		2 (13.3)	4 (57.2)	0.05
Bacteraemia and sepsis, n (%)		3 (20.0)	2 (28.6)	1.0
Hepatic toxicity, n (%)		1 (6.7)	0 (0.0)	1.0

Abbreviations: CLARA (Clofarabine+Cytarabine); CR (complete response); CRi (complete response with incomplete recovery); ELN (Eurpean Leukemia Net); IQR (interquartile range); OS (overall survival); PR (partial response); RD (refractory disease); RFS (relapsed free survival); SCT (stem cell transplantation).

patients treated in the third line it was equal to 0 months in both groups ((p-value: 0.10).

As shown in **table 1**, CR rate in the second-line therapy cohort was 53% and 28% in the CLARA and control (p-value: 0.09), respectively, while ORR was 67% and 44% (p-value: 0.14). Median OS was 8 and 7 months (p-value: 0.98) in the CLARA and the control group, respectively (**figure 1**); on the other side, median RFS was 3 and 0 months (p-value: 0.02), respectively. As shown in **table 2**, CR rate in the third-line therapy cohort was 29% and 13% in the CLARA and control (p-value: 0.57), respectively, while ORR was 29% and 20% (p-value: 1.0). Median OS was 2 and 3 months (p-value: 0.52), respectively. A median RFS of 0 was recorded in both groups. Patients who received allogeneic transplantation after second-line therapy were 20% and 6% in the CLARA and control group (p-value: 0.31), respectively while patients who received allogeneic transplantation after third-line therapy were 29% and 20% in the CLARA and control group (p-value: 1.00), respectively. Among the patients who underwent allogeneic SCT after second-line treatment, out the 2 treated within the control group one was in CR, and one in CR with incomplete recovery (CRi) whereas out the 3 treated with CLARA 2 were in CR and one in partial remission (PR). All of them achieved CR after transplant, and transplant-related mortality (TRM) was 0%. Among the patients who underwent allogeneic SCT after third-line treatment, out the 3 treated within the control group one was in CR, and two had a refractory disease (RD) whereas the 2 patients treated with CLARA were both in CR. Among the 3 patients treated within the control group, 2 achieved CR after transplant, and one still showed RD whereas among the 2 patients treated with CLARA one confirmed his CR while one died soon after transplant for TRM. Safety profile was good, with a tendentially higher rate of reversible (i.e., <2 weeks) hepatotoxicity cases after second-line therapy in the CLARA group (33% VS. 9%; p-value: 0.09) and a higher rate of pneumonia after third-line therapy in the CLARA group (57% VS. 13%; p-value: 0.05).

Comparison of our findings with those described in the literature showed that CR and OS rates were similar, whereas RFS was slightly lower in our cohort. Potential explanations could be the low percentage of patients exposed to chemotherapy as a bridge to allogeneic transplantation, as well as the retrospective design of our study which selected patients tendentially less fit than those described in prospective studies. Our data substantially confirm the potential effectiveness of CLARA in patients with R/R AML. In fact, even though a statistically significant improvement over other frequently prescribed salvage regimens was not demonstrated, our findings suggest a potential positive trend in terms of improvement in both CR, ORR, and

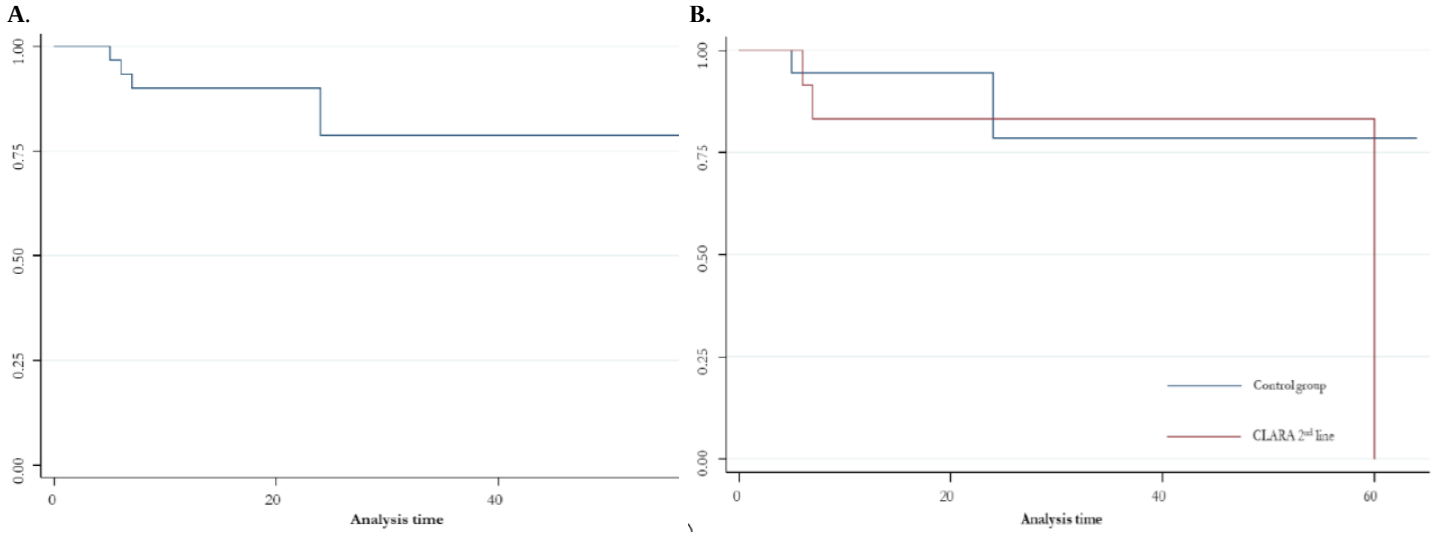

Figure 1. a) Kaplan Mayer survival curves for patients treated in second line in the overall population **b)** Kaplan Mayer survival curves for patients treated in second line in the population stratified according to their treatment with CLARA or with the control group

RFS within a real-life setting. When considering that the main goal in R/R AML, regardless of salvage regimens, is to perform allogeneic transplantation as earliest as possible, CLARA may represent a valid option in this setting especially in patients with a contraindication for or resistant to anthracycline-containing regimens.

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