Amsacrine combined with High Dose Cytarabine in Relapsed/Refractory Acute Myeloid Leukemia (rrAML)

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INTRODUCTION

The outcome of patients with rrAML is dismal, and effective treatment options are still desperately needed. To date no salvage treatment proved to be superior to the others. In this study, we retrospectively analyzed -in one single Centre- the efficacy and the safety of Amsacrine in combination with HD Cytarabine in rrAML.

Patient's Characteristics	N (%)
Total	39
Median Age [range], years	51.8 [15.5 – 69.6]
Sex	
Male	25 (64.1)
Female	14 (35.9)
Type of AML	
De Novo	29 (74)
Secondary	10 (26)
Post MDS/MPN	7 (18)
Therapy-related	3 (8)
Relapsed/Refractory	
Relapsed	27 (69.2)
1 previous line	25 (92.6)
2 previous line	2 (7.4)
Refractory	12 (30.8)
Previous AuSCT or AlloSCT	
Yes	11 (44%)
No	16 (66%)
Previous HiDAC	
Yes	15 (38.5)
No	24 (61.5)

OBJECTIVES & METHODS

Between January 2001 and September 2016, 39 rrAML patients were treated with Cytarabine (1gr/m² every 12h, D1-6) and Amsacrine (150mg/m² every 24h , D5-7). Primary objective was Overall Rate Response (ORR), defined as the proportion of patients who achieved Complete Remission (CR) or CRi (CR with incomplete recovery). Secondary objectives included Event Free Survival (EFS), Overall Survival (OS) and % of patients able to be bridged to Allogeneic Stem Cell Transplantation (AlloSCT).

RESULTS

Median age at relapse was 51.8 (15.5 - 69.6), with 27 (69.2%) relapsed and 12 (30.8%) refractory patients. ORR was 76.9% (CI: 61.7 - 87.4), with 22 patients that achieved a CR (56.4%; 95% CI: 41.0 - 70.7) and 8 a CRi. Median OS was 15.7 months (1.1 - 114.9). Median EFS was 12.2 months (0.9 - 95.5). 22 patients (51.3%) were bridged to AlloSCT in CR2. MRC Cytogenetic Risk Category stratification retained its prognostic significance for both OS (P=0.0291) and EFS (P=0.0280). CD15 expression was significant for inferior OS (P=0.0149) while CD117 expression was significant for better OS (P=0.0160). The Charlson Age-Comorbidity Index score (CACI) was strongly correlated with OS (P=<0.0001) and cardiac comorbidities strongly predicted a lower OS (P=0.0031). Treatment related mortality at 30- and 42-days was 5 and 13%.

RESPONSES	Pts with rrAML (N=39)
ORR (%)	76,9 [CI: 61.7-87.4]
• CR (%)	• 56,4 [CI: 41.0–70.7]
• CRi (%)	• 20,5 [CI: 9.3 – 38.1]
• CR MRD Neg (%)	• 20,7 [CI: 9.9 – 38.4]
Med OS (Mos)	15,7 (1,1-114,9)
Med EFS (Mos)	12,2 (0,9-95,5)

KEY MESSAGES

- **Highly Effective:** ORR 76.9% (CR 56.4%, 20.7% CR-MRD Neg), Median EFS and OS: 12.2 months and 15.7 months, 22 patients (51.3%) bridged to AlloSCT in CR2.
- **Good Toxicity Profile:** 36 (23-85) days of median hospitalization duration, 20.5% needed intensive care, 5.13% TRM at 42days,
- **Predictive Factors for OS:** Cytogenetics Risk Category, Presence of Cardiovascular Comorbidities, CD15 and CD117 Expression, Hb level

Prognostic factor	ORR (%)	P-Value	EFS (months)	P-Value	OS (months)	P-Value
Caucasian						
Yes	85.19	0.14	NR	0.04	28.1	0.1571
No	63.64		2.0		4.3	
Cytogenetic Group MRC						
Fav	100	0.22	NR	0.03	13.8	0.03
Int	81.82		89.8		41.5	
Adv	63.64		4.2		7.0	
CD15						
Pos	80.95	0.31	3.1	0.08	4.0	0.01
Neg	50		11.4		28.1	
CD117						
Pos	80	0.96	12.2	0.29	28.1	0.02
Neg	79.17		4.4		5.7	
Hb (g/dL)						
< 9.9	66.67	0.01	8.0	0.08	6.5	0.04
≥ 9.9	90.0		NR		41.5	
EPI Score						
Fav	100	0.12	NR	0.03	13.8	0.89
Int	100		NR		15.7	
Adv	70.37		6.6		10.3	
Cardiac Comorbidities						
Yes	82.1	0.41	4.4	0.36	5.4	0.003
No	70.0		89.8		29.2	
Setting of Treatment						
Relapse	80.77	0.68	NR	0.09	17.5	0.31
Refractory	75		4.9		6.7	
RFI (months)						
< 6	71.43	0.38	4.9	0.08	6.7	0.43
> 6	83.33		NR		17.5	

Table IX. Prognostic Factors for CR, EFS, OS. NR = Not reached

CONCLUSION

The high response rate (56% CR - 77% ORR) and the low toxicity profile observed in our study suggests That HD-ARA-c combined with AMSACRINE is an effective salvage regimen that allows bridge to AlloSCT in 51% of the patients.