



Outcome with Intensive Chemotherapy Compared to Hypomethylating Agent Based Induction in Elderly Patients with Newly Diagnosed Favorable Risk Acute Myeloid Leukemia

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Abstract

- In this retrospective study, clinical, demographic, and genomic data were collected on patients aged ≥70 years (yrs) with favorable risk (ELN 2017) acute myeloid leukemia (FR-AML) to compare outcomes with intensive and non-intensive induction regimens
- Patients receiving intensive chemotherapy (IC; n= 35) were significantly younger than those on hypomethylating agent (HMA; n=16) alone or HMA-venetoclax combination (HMA-Ven; n=7)
- Both IC and HMA-Ven led to significantly better composite complete remission (cCR- CR+CRi) rates compared to HMA alone (cCR- IC vs. HMA-Ven vs. HMA- 69% vs. 71% vs. 31%; p= **0.032**)
- Patients on IC had numerically higher 30 and 60-day mortality rates, although difference between groups was not statistically significant
- Median overall survival (mOS) was significantly better with IC compared to HMA alone (25.5 vs.17.5 months; p= **0.039**), although it was not independent predictor on multivariate analysis adjusting for age, core binding factor (CBF) positivity and allogeneic stem cell transplant (allo-SCT) status
- A multicenter study with larger sample size is ongoing to further address this research question

Background

- Elderly fit patients with FR-AML are traditionally treated with IC (most commonly 7+3) for induction, based on data extrapolated from studies in patients <60 yrs old
- However, advanced age, comorbidities, and poor performance status significantly increase the risk of treatment-related complications and mortality
- A recent single center study (*Lachowiez et al. 2020*) in patients with NPM1-mutant AML (>65 yrs) reported improved outcome with HMA-Ven compared to HMA alone
- However, real world evidence lacks on efficacy and long-term outcomes of intensive and non-intensive induction strategies in very elderly patients (≥70 yrs) with FR-AML

Methods

- This was a retrospective clinical study
- All patients aged ≥70 yrs with FR-AML (ELN 2017), treated at Moffitt Cancer Center were eligible for inclusion
- Clinical, demographic, and genomic data were collected by review of medical records of eligible patients
- Patients who received IC, HMA-Ven, or HMA alone as induction treatment were included in the final analyses
- Descriptive statistics was used to compare categorical variables
- Response to therapy was assessed using the ELN 2017 criteria
- We used Kaplan-Meier statistics to estimate time to event endpoints and multivariate analysis was done with Cox Regression Hazards model
- All statistical analyses were performed in SPSS (v.26)

Results

- Our study included 58 patients (IC- 35, HMA- 16, HMA-Ven-7) [Table 1]
- Median age at diagnosis was 75 yrs; Patients in IC group were significantly younger (74 yrs), compared to HMA (76 yrs) or HMA-Ven (77 yrs) (p= 0.007)
- No significant differences between groups were noted in gender or race distribution, ECOG performance status, type of AML (de novo vs. secondary), proportion of CBF-AML, white blood cell (WBC) or bone marrow blast counts, and frequency of recurrent mutations
- Median duration of follow up was 36.9 months
- Patients on IC and HMA-Ven experienced significantly better rates of cCR (CR+CRi) compared to HMA alone (cCR- IC vs. HMA-Ven vs. HMA- 69% vs. 71% vs. 31%; p= **0.032**); Overall response was 72% with IC, 85% on HMA-Ven, and 31% with HMA alone [Table 2]
- Nine patients (7 within 30 days) died within 60 days of induction- majority (n=6) in IC group
- Six patients (3 post-relapse) from IC group underwent allo-SCT

Table 1. Baseline Characteristics of the Study Population

Variables	Total (n=58)	Intensive Chemo (n=35)	HMA alone (n=16)	HMA-Ven (n=7)	p value
<i>Patient Related Variables</i>					
Median age at diagnosis, years (range)	75 (70-92)	74 (70-84)	76 (71-85)	77 (75-92)	0.007
Male Gender, n (%)	34 (59%)	22 (63%)	8 (50%)	4 (57%)	0.697
White Race, n (%)	55 (95%)	33 (94%)	16 (100%)	6 (86%)	0.547
Performance status, n (%)					0.595
ECOG 0-1	52 (91%)	33 (94%)	12 (80%)	7 (100%)	
ECOG ≥ 2	5 (9%)	2 (6%)	3 (20%)	0 (0%)	
<i>Disease Related Variables</i>					
Type of AML, n (%)					0.757
De novo	43 (74%)	25 (71%)	13 (81%)	5 (71%)	
Secondary	15 (26%)	10 (29%)	3 (19%)	2 (29%)	
Cytogenetics, n (%)					0.181
Core binding factor AML	25 (43%)	15 (43%)	9 (56%)	1 (14%)	
t (8;21)	12 (23%)	6 (17%)	6 (38%)	0 (0%)	
Inv (16)	13 (24%)	9 (26%)	3 (18%)	1 (14%)	
Normal	33 (57%)	20 (57%)	7 (44%)	6 (86%)	
Median blast count (%) at diagnosis	50 (0-94)	57 (0- 94)	34 (3- 80)	65 (9-81)	0.104
Median WBC count at diagnosis (x 10 ⁹ /µL)	5.75 (0.2- 162.34)	7.20 (0.2-162.34)	2.82 (1.20-86.34)	3.20 (1.04-41.64)	0.094
Common recurrent somatic mutations, n (%) *					
NPM1	29 (63%)	17 (59%)	6 (60%)	6 (86%)	0.418
CEBPA	5 (14%)	4 (18%)	1 (14%)	0 (0%)	0.503
IDH1	2 (6%)	0 (0%)	1 (11%)	1 (14%)	0.356
IDH2	4 (13%)	1 (6%)	2 (22%)	1 (14%)	0.530

* Percentages calculated based on number of evaluable patients

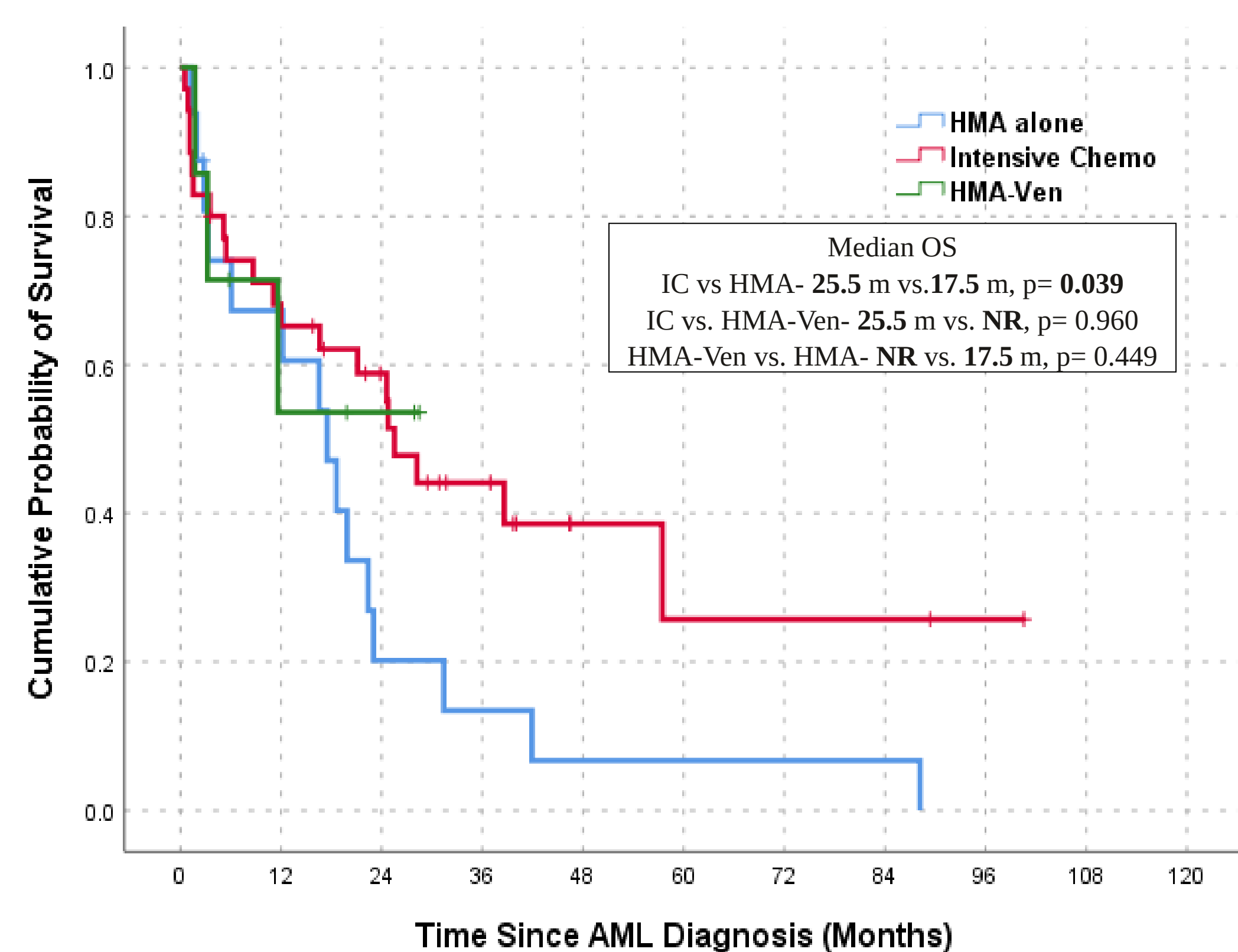
Results

Table 2. Treatment Outcomes with Different Induction Regimens

Outcome Measures	Total (n=58)	Intensive Chemo (n=35)	HMA alone (n=16)	HMA- Ven (n=7)	p value
Best response to induction therapy, n (%)*					
Composite CR (CR+ CRi)	34 (59%)	24 (69%)	5 (31%)	5 (71%)	0.032
CR	22 (38%)	17 (49%)	4 (25%)	1 (14%)	0.110
CRi	12 (21%)	7 (20%)	1 (6%)	4 (57%)	
PR	2 (3%)	1 (3%)	0 (0%)	1 (14%)	
SD	15 (26%)	6 (17%)	9 (56%)	0 (0%)	
30 day mortality, n (%)	7 (12%)	6 (17%)	1 (6%)	0 (0%)	0.325
60 day mortality, n (%)	9 (16%)	6 (17%)	2 (13%)	1 (14%)	0.896
Relapse, n (%)					
Total	20 (34%)	12 (34%)	6 (38%)	2 (29%)	0.921
Early (<12 months)	10 (17%)	6 (17%)	2 (13%)	2 (29%)	
Late (>12 months)	10 (17%)	6 (17%)	4 (25%)	0 (0%)	
Relapse free survival, median (months)	9.9	8.4	13.7	6.4	0.219
Allogeneic SCT, n (%)	6 (10%)	6 (17%)	0 (0%)	0 (0%)	0.114

* Percentages calculated based on number of evaluable patients

Figure 1. Overall Survival of Patients on Treatment with Different Induction Regimens



Results

- In our study, 34% patients relapsed, with comparable early and late relapse rates across groups; Median relapse free survival was 9.9 months in evaluable patients, with no significant difference between groups
- Patients receiving IC as induction had a significantly prolonged mOS than those on HMA alone (25.5 vs.17.5 months; p= **0.039**) [Figure 1]
- On multivariate analysis adjusting for age at diagnosis, CBF-AML, and allo-SCT status, receipt of IC induction was not independent predictor of survival (HR 0.68, 95% CI: 0.31- 1.47; p= 0.324) compared to HMA alone
- In patients with CBF-AML (n=24), IC group showed a trend towards improved mOS vs. HMA alone (Not reached vs. 23 months; p= 0.066)
- Differences in mOS between IC vs. HMA-Ven (25.5 months vs. not reached; p= 0.960) and HMA-Ven vs. HMA alone (Not reached vs. 17.5 months; p= 0.449) did not reach statistical significance
- Overall, 24% patients in IC group were alive at 5 years, compared to 7% with HMA

Conclusions

- Induction treatment with IC and HMA-Ven led to significantly better cCR rates compared to HMA alone in elderly (≥70 yrs) patients with FR-AML
- No significant difference was observed in early mortality rates (at 30 and 60 days), relapse rates, and relapse free survival between treatment groups
- Patients receiving IC had an improved mOS compared to HMA alone, although it was not independent predictor on multivariate analysis
- In patients with CBF-AML, induction with IC showed a trend towards improved survival compared to HMA alone
- A multicenter expansion of this project with larger sample size is currently ongoing to further address the research question

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