Clinical outcomes of decitabine and the role of WT-1 expression as a surrogate prognostic maker for patients with elderly acute myeloid leukemia

Byung-Sik Cho, Seung-Hwan Shin, Sung-Eun Lee, Sung-Soo Park, Jae-Ho Yoon, Seung-Ah Yahng, and Hee-Je Kim
Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital,
Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Catholic BMT Center

Abstract

- Background: Since several clinical trials suggested the better outcomes compared to those of conventional treatments, decitabine has been a standard of care for patients with elderly acute myeloid leukemia (eAML). However, the real-world clinical outcomes and useful prognostic marker for these patients are scarcely investigated.
- Methods: We analyzed the clinical outcomes of 85 eAML patients who received decitabine from Oct 2011 and Aug 2017 at our institution. In addition, we investigated the role of WT-1 gene for outcomes of 59 patients (WT-1 cohort) available with its qRT-PCR data.
- Results: At diagnosis, the median age of patients was 73 (range, 64-86) years. Of them, 22 (25.9%) and 15 (17.5%) patients had secondary etiology and adverse cytogenetic risk, respectively. Patients received median 5 cycles of decitabine (range, 1-32). They achieved best response after 4 (range, 1-13) cycles of decitabine. The overall response (OR) and complete response (CR; including incomplete CR and CR without platelet recovery) rates were 43.5% and 31.8%, respectively, with the median duration of response of 10.1 months (range, 0.4-28). The median overall survival (OS) of patients was 7.9 months. The OS rates of patients achieved CR, partial or marrow response, and no response were significantly different (88.4%, 50.3%, and 7.4% at 1 year, respectively; $P < 0.01$). When we further analyzed the outcomes of WT-1 cohort, the high WT-1 group (≥ 4500 copies/ 10^4 ABL at diagnosis) showed a significantly higher OS rate compared that of the low WT-1 group (51.8% vs. 38.5% at 1 year; $P = 0.02$). Of note, the WT-1 expression of patients who achieved CR significantly decreased at the time of response compared to that at the diagnosis ($P = 0.02$), whereas those who achieved PR or mR did not ($P = 0.06$).
- Conclusions: Our data showed the clinical efficacy and tolerability of decitabine for patients with eAML in real-world setting. In addition, the possible role of WT-1 as a surrogate marker to predict outcomes or estimate response by decitabine is suggested.

Background

- Since several clinical trials suggested the better outcomes compared to those of conventional treatments, decitabine (DAC) has been a standard of care for patients with elderly acute myeloid leukemia (eAML).
- However, the real-world clinical outcomes and useful prognostic marker for these patients are scarcely investigated
- Wilms tumor (WT)-1 gene (Haematologica 2016;101:627)
 - ✓ Implicated in various malignancies, including AML
 - ✓ Overexpressed in progenitor cells
 - ✓ Progression from MDS to AML
 - ✓ Reduced survival & increased relapse
 - ✓ Association with FLT3 mutations
 - ✓ WT-1 mutation
 - ✓ Chemo-resistance, FLT3-ITD and CEBPA, Younger age, and impaired OS and RFS
 - ✓ Interaction with the epigenetic modifiers TET2 and TET3 in AML

Objective

- To analyze the efficacy of DAC for eAML in real world
- To investigate the prognostic factor which can predict response and/or survival for eAML receiving DAC

Patients and Methods

- Enrolled patients: eAML patients over 65 years who received DAC between Oct 2011 and Aug 2017 at Catholic Hematology Hospital
- WT-1 Profile Quant kit ELN™ (Ipsogen, Marseille, France)
- Primary end points: response and overall survival
- Definition of response by modified 2003 IWG criteria
- Decitabine (DAC): median 5 cycles (range, 1-32)

Characteristics	Overall cohort (n=85)	WT-1 cohort (n=59)
Sex (Male)	45 (52.9%)	34 (57.6%)
Age, median (range)	73 (range; 64 – 86)	72 (range; 65 – 86)
ECOG PS (≥ 2)	12 (14.1%)	11 (18.6%)
HCT-CI (≥ 3)	52 (61.2%)	38 (64.4%)
WBC ($\times 10^6/l$), median (range)	7535 (range; 660 – 296870)	7550(range; 750 – 296870)
PB blast (%), median (range)	24.0 (range; 0 – 98)	30.0 (range; 0 – 98)
Platelet ($\times 10^9/l$), median (range)	64 (range; 5 – 457)	65 (range; 5 – 457)
Albumin (< 3.5 g/dl)	33 (38.8%)	21 (35.6%)
LDH ($> UNL$)	63 (74.1%)	49 (76.3%)
BM blast (%), median (range)	72 (range; 20.0 – 99)	79 (range; 20 – 99)
MRC / secondary / chemotherapy-related etiology	22 (25.9%)	16 (27.1%)
Favorable/Intermediate/Poor NCCN risk group	16 (18.8%) / 54 (63.5%) / 15 (17.5%)	15 (25.4%) / 31 (52.5%) / 13 (22.0%)
CEBPA (+)	10 / 61 (16.4%)	10 / 52 (19.2%)
NPM1 (+)	18 / 65 (27.7%)	16 / 56 (28.6%)
FLT3-ITD (+)	9 / 66 (13.7%)	6 / 57 (10.5%)

Results

Overall cohort (n=85): Response

- Initial response
 - after 3 cycles (range, 1-11)
- Best response
 - after 4 cycles (range, 1~13)

Outcomes	Rate (%)
OR	43.5%
CRc	31.8%
Duration of response	10.1 mo

Characteristics	Univariate analysis			
	OR rate	P	CRc rate	P
Sex (Male vs. Female)	42.2% vs. 45.0%	0.97	31.1% vs. 32.5%	1.00
Age (≤ 70 yrs vs. > 70 yrs)	48.3% vs. 41.1%	0.69	41.4% VS. 26.8%	0.26
ECOG PS (<2 vs. ≥ 2)	46.6% vs. 25.0%	0.28	32.9% vs. 25.0%	0.83
HCT-CI (< 3 vs. ≥ 3)	36.4% vs. 48.1%	0.40	21.2% vs. 38.5%	0.15
WBC ($< 10 \times 10^9/l$ vs. $\geq 10 \times 10^9/l$)	45.5% vs. 41.5%	0.88	31.8% vs. 31.7%	1.00
PB blast (<20 % vs. ≥ 20 %)	43.2% vs. 43.8%	1.00	35.1% vs. 29.2%	0.73
Platelet ($<50 \times 10^9/l$ vs. $\geq 50 \times 10^9/l$)	45.5% vs. 42.3%	0.95	33.3% vs. 30.8%	0.99
Albumin (< 3.5 g/dl vs. ≥ 3.5 g/dl)	33.3% vs. 50.0%	0.20	24.2% vs 36.5%	0.34
LDH ($\leq UNL$ vs. $> UNL$)	40.9% vs. 44.4%	0.97	31.8% vs. 31.7%	1.00
BM blast (< 30 % vs. ≥ 30 %)	50.0% vs. 42.7%	0.92	40.0% vs. 30.7%	0.82
Etiology (de novo vs. other)	49.2% vs. 27.3%	0.12	34.9% vs. 22.7%	0.43
NCCN risk group (Fav/Int vs. poor)	44.3% vs. 40.0%	0.97	32.9% vs. 26.7%	0.87

Overall cohort (n=85): Survival

- Median OS: 7.9 months
- OS rate at 1 year: 38.8%
- Early mortality at Day 30: 9.4%

Characteristics	Univariate analysis OS rate at 1 year	P
Sex (Male vs. Female)	46.8% vs. 34.7%	0.54
Age (≤ 70 yrs vs. > 70 yrs)	58.6% vs. 32.0%	0.10
ECOG PS (<2 vs. ≥ 2)	44.7% vs. 12.5%	0.01
HCT-CI (< 3 vs. ≥ 3)	36.1% vs. 43.0%	0.70
WBC ($< 10 \times 10^9/l$ vs. $\geq 10 \times 10^9/l$)	41.9% vs. 38.3%	0.19
PB blast (<20 % vs. ≥ 20 %)	39.3% vs. 40.1%	0.40
Platelet ($<50 \times 10^9/l$ vs. $\geq 50 \times 10^9/l$)	45.3% vs. 37.1%	0.45
Albumin (< 3.5 g/dl vs. ≥ 3.5 g/dl)	31.1% vs. 46.0%	0.13
LDH ($\leq UNL$ vs. $> UNL$)	40.4% vs. 40.0%	0.39
BM blast (< 30 % vs. ≥ 30 %)	37.5% vs. 40.1%	0.22
Etiology (de novo vs. other)	45.2% vs. 31.8%	0.30
NCCN risk group (Fav/Int vs. poor)	43.3% vs. 26.7%	0.09

WT-1 cohort (n=59): Response and survival

- Median WT-1 levels at diagnosis
 - ✓ 4500 copies/ 10^4 ABL copies = 0.45

Comparison of response or survival by WT-1 levels at diagnosis

Characteristics	Univariate analysis	P	Multivariate analysis	P
	OS rate at 1 year		HR (95% CI)	
Age (<70 vs. ≥ 70)	55.2% vs. 32.0%	0.09	2.38 (1.23-4.76)	0.01
ECOG (<2 vs. ≥ 2)	44.7% vs. 12.5%	0.01	2.83 (1.29-6.23)	0.01
RISK(Favorable/Int vs. Poor)	51.4% vs. 35.1%	0.08	1.62 (0.75-3.49)	0.22
WT1 (< 0.45 vs ≥ 0.45)	38.5% vs. 51.8%	0.02	0.42 (0.22 – 0.81)	< 0.01

Conclusions

- The clinical efficacy and tolerability of DAC for patients with eAML in real-world setting was shown.
- The previously noticed patient or disease-related factors did not predict the therapeutic outcomes in our cohort. However, it should be interpreted cautiously owing to a relatively small number of analyzed patients.
- The possibility of WT-1 as a novel surrogate marker for eAML patients receiving DAC was suggested.
- Several reports showed mutated WT-1 gene is associated with the hypermethylation of some genes in AML. However, there is no study of the correlation between WT-1 overexpression and DNA hypermethylation. In vitro and vivo studies are needed.
- Further prospective studies using a larger cohort are needed to confirm our results.