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ORAL ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Optimization of Idarubicin and Cytarabine Induction Regimen with Homoharringtonine for Newly Diagnosed AML Based on the Peripheral Blast Clearance Rate: First Result of the Multicenter, Randomized, Phase 3 Trial (RJ-AML 2016)

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Background: Combination of idarubicin and cytarabine (IA) is still the basis of induction treatment for acute myeloid leukemia (AML). As previous reported in RJ-AML 2014 trial [1], day 5 peripheral blast clearance rate (D5-PBCR) can be used as an indicator of early treatment response, and for patients in the D5-PBCR (+) group, addition of homoharringtonine (HHT) to traditional IA induction showed good efficacy and safety. To further verify the efficacy in long-term outcome, we designed the RJ-AML 2016 trial. Here we report the latest response and survival results.

Patients and Methods: The RJ-AML 2016 trial is a multicenter, randomized, phase 3 clinical trial, conducted to evaluate the efficacy of HHT in newly diagnosed young AML. Patients in D5-PBCR(+) group was eligible for addition of HHT, and were assigned in a 1:1 ratio, either to the intervention or control group. The primary end point was event-free survival (EFS). The secondary end points were composite complete remission (CR or CR with incomplete hematologic recovery), early death rate, measurable residual disease, drug toxicity, and safety. We hypothesized the 3-year EFS rate may increase from 30% to 50%, therefore the sample size of patients who enter randomization should be 250. Based on historical data, the rate of D5-PRCR(+) was 43%. Assume that 10% of patients may lost to follow-up, at least 638 eligible patients were needed. All patients enrolled in this study received induction regimen same as the RJ-AML 2014 trial. D5-PRCR(+) patients who assigned to the intervention group received additional chemotherapy (HHT 2 mg/m ^{2} on days 6-10). Favorable cytogenetic/molecular risks group received four courses of the HiDAC for consolidation. Patients with intermediate and unfavorable risks were recommended for allogeneic hematopoietic stem-cell transplantation. The trial is registered in the Chinese Clinical Trial Register, number ChiCTR-OIC-16007764.

Results: From December 7, 2016, through April 29, 2023, a total of 747 patients underwent screening, 649 were included in the intention-to-treat (ITT) population and received IA induction from 6 sites in China. D5-PBCR were analyzed in 647 patients and 275 (42.5%) had D5-PBCR (+). Of the 275 D5-PBCR (+) patients, 145 were allocated to the intervention group, while 20 patients withdraw, of which 4 patients received additional FLT3 inhibitor and 16 cases continued IA induction; of the 130 patients allocated to the control group, 5 discontinued the IA regimen on day 6 or 7. Of the 372 D5-PBCR (-) patients, 2 patients discontinued IA.

Baseline characteristics, including age, sex, blast counts in bone marrow, and cytogenetic parameters, were similar between two groups. While patients in D5-PBCR (-) group had higher white blood cell counts before treatment. Patients with *CBFβ-MYH11* fusion, *NPM1* and *CEBPA* bZIP mutations were more sensitive to IA induction. Meanwhile, high-risk gene mutations including *ASXL1*, *RUNX1*, *TP53* and *U2AF1* were more common in D5-PBCR (+) group. Details were showed in table.

The overall composite CR rate after one course of induction was 73.2% in the ITT cohort. For patients in D5-PBCR (-) and D5-PBCR (+) groups, the CR rates were 82.8% and 60.4% , respectively (P<0.001). In the ITT cohort of D5-PBCR (+) group, CR rates were 51.1% and 68.3% for control and intervention arm, respectively (P=0.0046). In the Per-Protocol (PP) cohort, CR rates were 52.8% and 71.2% for IA and IA+HHT arm, respectively (P=0.0027). The overall early mortality rate was 4.9% in whole cohort, which were similar between two treatment arms.

The last follow-up time was April 2023. Patients in the PP cohort who enrolled before April 2022 were included in this survival analysis (n=486), and the median duration of follow-up was 23.4 months. The median EFS was 40.6 months in the PP cohort,

which showed significant difference between D5-PBCR (-) and D5-PBCR (+) groups [D5-PBCR (-): not reached, D5-PBCR (+): 16.0±1.9 months, P<0.001]. For patients in the D5-PBCR (+) group, no significant difference was found in 3-year EFS till the latest follow-up. While, the 3-year EFS was improved from 34.0±5.5% to 47.1±6.1% with the addition of HHT (*P*=0.086). Conclusion: Current analysis indicated that addition of HHT can benefit young AML patients in the D5-PBCR (+) group. Complete follow-up combining with cytogenetic-molecular information can provide more reliable results.

1. Zhang Y, et al. Am J Hematol. 2022;97(1):43-51.

Disclosures No relevant conflicts of interest to declare.

Characteristics	All Patients (n=647)	D5-PBCR (-) (n=372)	D5-PBCR (+) (n=275)	*P*
Age, years	44 (33–53)	42 (33–53)	45 (35–53)	0.27
Sex				0.86
Male	339 (52.4%)	196 (52.7%)	143 (52.0%)	
Female	308 (47.6%)	176 (47.3%)	132 (48.0%)	
White blood cell count, $\times 10^9$/L	13.5 (3.6-47.2)	19.2 (4.3–58.6)	8.5 (2.8–33.5)	**0.01**
Blasts in bone marrow, %	63.5 (43.5–79.0)	65 (43.5–81)	61 (41.5–76)	0.12
Cytogenetics, No[#]				0.47
Favorable	97 (16.1%)	58 (16.7%)	39 (15.2%)	
Intermediate	399 (66.2%)	233 (67.2%)	166 (64.8%)	
Unfavorable	107 (17.7%)	56 (16.1%)	51 (20.0%)	
Gene Fusion				
RUNX1-RUNX1T1	60/615 (9.8%)	30/355 (8.5%)	30/260 (11.5%)	0.202
CBFβ-MYH11	44/615 (7.2%)	32/355 (9.0%)	12/260 (4.6%)	**0.037**
KMT2A fusion	38/612 (6.2%)	24/354 (6.8%)	14/258 (5.4%)	0.493
Gene mutation				
NPM1	138/616 (22.4%)	99/355 (27.9%)	39/261 (14.9%)	**<0.001**
FLT3–ITD	112/615 (18.2%)	68/355 (19.2%)	44/260 (16.9%)	0.479
CEBPA bZIP	120/614 (19.5%)	85/354 (24.0%)	35/260 (13.5%)	**0.001**
ASXL1	26/415 (6.3%)	10/243 (4.1%)	16/172 (9.3%)	**0.032**
RUNX1	34/415 (8.2%)	11/243 (4.5%)	23/172 (13.3%)	**0.001**
TP53	14/415 (3.4%)	3/243 (1.2%)	11/172 (6.4%)	**0.004**
U2AF1	12/415 (2.9%)	3/243 (1.2%)	9/172 (5.2%)	**0.033**
Treatment response after one induction				
Composite CR, No.(%)	474 (73.2%)	308 (82.8%)	166 (60.4%)[$]	**<0.001**
Early Death, No. (%)	32 (4.9%)	15 (4.2%)	17 (5.8%)	0.21

[#] 25 patients had missing cytogenetics results in D5-PBCR(-) group, and 19 in the D5-PBCR(+) group.
[$] CR rate of the ITT cohort in the D5-PBCR(+) group: IA, 67/130 (51.5%); IA+HHT, 99/145 (68.3%); P=0.0046
CR rate of the PP cohort in the D5-PBCR(+) group: IA, 66/125 (52.8%); IA+HHT, 89/125 (71.2%); P=0.0027

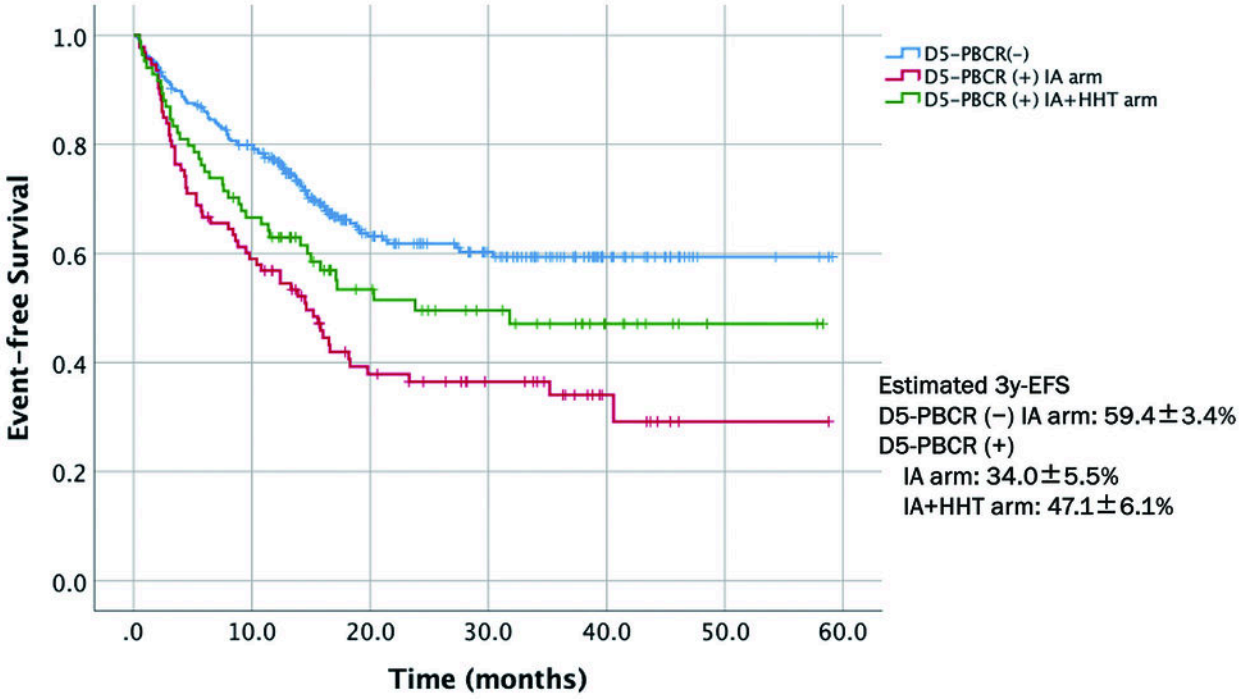

Figure 1

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