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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Cytoreductive Chemotherapy in Induction Therapy Plays a Key Role in the Prognosis of Patients with Low-Risk Acute Promyelocytic Leukemia

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Introduction:
Despite the success for low-risk acute promyelocytic leukemia (APL) in the all-trans retinoic acid (ATRA) plus arsenicals era, several important clinical issues continue to account for treatment failure including early death (ED) and disease relapse. The present study was conducted to explore the potential role of cytoreduction during induction therapy on prognosis.

Methods:
All consecutive low-risk APL patients who received ATRA plus arsenic for induction and consolidation therapy at the Peking University People's Hospital, Peking University Institute of Hematology, between February 2014 and September 2021, were analyzed. Kaplan-Meier was used to estimate relapse rates and OS. Exploration of factors associated with relapse was based on Cox proportional hazards regression model.

Results:
Here 282 patients were diagnosed with low-risk APL and received ATRA plus arsenic as an induction and consolidation therapy. During induction therapy, six patients died early. Nine patients were withdrawn after induction therapy. Of the 282 patients evaluable for OS, the 5-year OS was 97.9%. Of the 267 patients evaluable for relapse, 14 patients (5.2%) relapsed throughout follow-up, with the 5-year cumulative relapse incidence of 5.9%. The median time to relapse, including hematological, molecular and extramedullary relapse, was 18.5 (IQR 12.25-24.5, range 6.2-52.0) months after hematological CR. After induction therapy, all 276 evaluable patients (100%) achieved hematological CR.

Cytoreduction therapy, including hydroxycarbamide, anthracyclines and cytarabine during induction therapy was administrated based on the 2018 Chinese APL guidelines. Given the unavailability and inconveniences of intravenous chemotherapy at some stage in the COVID-19 pandemic, our center explored the routine of oral etoposide as cytoreductive therapy from January 2020. Etoposide was administered to patients with a WBC count of 3.2-9.8×10 ^{9}/L at diagnosis. The cumulative mean dose of etoposide was 706.5 mg (range, 150-1700 mg) during the induction therapy. In terms of different cytoreduction therapies, 86 patients were administered with hydroxycarbamide (30.5%), 113 with anthracyclines or cytarabine (40.1%), 31 with etoposide (11.0%), and 52 with no cytoreductive therapy (18.4%) during induction therapy. We previously explored that promyelocytic leukemia retinoic acid receptor alpha (PML-RARA) transcript level of 6.5% or more after induction therapy was associated with a subsequent risk of relapse.

Compared to patients with no cytoreduction therapy or only hydroxycarbamide during induction therapy, the incidence of *PML-RARA* transcript levels of ≥6.5% was significantly decreased at the end of induction therapy in those who received anthracyclines/cytarabine and etoposide (27.5% *vs.* 26.2% *vs.* 15.5% *vs.* 0%, $P = 0.003$, Table 1). Notably, 2-year cumulative relapse rates were significantly lower in the anthracyclines/cytarabine treatment group and the etoposide treatment group (3.962% *vs.* 8.861% *vs.* 1.887% *vs.* 0%, $P = 0.040$, Table 1). The hydroxycarbamide treatment group did not decrease the relapse rate compared to the no cytoreduction group (11.4% *vs.* 5.9%, $P = 0.289$). To estimate RFS, the hydroxycarbamide

treatment group and the no cytoreduction treatment group were merged to create a single group (the H/N group, 5-year RFS, 90.391%). Compared with the H/N group, the anthracyclines/cytarabine treatment group and the etoposide treatment group showed improved 2-year RFS (93.064% *vs.* 98.113% *vs.* 100.0%, $P = 0.046$, Figure 1). Multivariate Cox regression analysis revealed that myeloblasts in bone marrow at diagnosis, Leukocytosis during induction therapy, *PML-RARA* of $\geq$6.5%, and anthracyclines/cytarabine cytoreductive treatment were associated with a subsequent risk of relapse.

Conclusions:

In summary, the present study indicated that cytoreductive chemotherapy had a dual effect of both cytoreduction and prevention of relapse in low-risk APL. Oral etoposide as cytoreduction therapy combined with oral ATRA plus RIF is expected to be a regimen with low relapse, good tolerance and great convenience. A prospective, randomized, controlled, interventional study on oral etoposide versus intravenous daunorubicin for cytoreductive chemotherapy in induction therapy in patients with low-risk APL is now going on (NCT05832320).

Disclosures No relevant conflicts of interest to declare.

Table 1. Responses and outcomes of different cytoreduction during induction therapy.

	Cytoreductive therapy (n = 282)				
	None (n = 52)	Hydroxycarbamide (n = 86)	Anthracyclines or cytarabine (n = 113)	Etoposide (n = 31)	*P*
Age, years, median (range)	43.5 (13.0-66.0)	40.0 (14.0-79.0)	38.0 (18.0-70.0)	48.0 (17.0-67.0)	0.50
Male, n (%)					
WBC count, × 10⁹/L, median (range)	1.31 (0.01-7.84)	1.56 (0.34-8.40)	1.70 (0.30-9.79)	1.44 (0.34-9.82)	0.325
PLT count, × 10⁹/L, median (range)	28.5 (3-201)	32.5 (2-189)	28.0 (2-179)	29.0 (2-203)	0.107
PML-RARA type, n (%)					0.250
Long	34 (65.4)	55 (64.0)	73 (64.6)	19 (61.3)	
Short	8 (15.4)	14 (16.3)	16 (14.2)	10 (32.3)	
Variant	10 (19.2)	17 (19.8)	24 (21.2)	2 (6.5)	
FLT3-ITD gene positive at diagnosis, n (%)	5 (9.6)	13 (15.1)	6 (19.4)	15 (13.3)	0.646
Complex chromosomal abnormalities,n (%)	9 (17.3)	12 (14.0)	19 (16.8)	5 (16.1)	0.942
Myeloblast at diagnosis, n (%)	21 (40.4)	30 (34.9)	42 (37.2)	13 (41.9)	0.873
WT1 (%), median (range)	54.4 (1.0-145.5)	51.5 (2.3-556.8)	55.0 (1.1-157.5)	62.3 (1.8-214.7)	0.644
PRAME (%), median (range)	7.2 (1.2-696.4)	10.1 (0.3-398.0)	7.8 (0.5-450.0)	18.2 (0.9-268.3)	0.890
ED, n (%)	1 (1.9)	2 (2.3)	3 (2.6)	0 (0.0)	0.840
Leukocytosis during induction, n (%)	2 (3.8)	43 (50.0)	100 (88.5)	20 (64.5)	-
Differentiation syndrome, n (%)	0 (0.0)	19 (22.1)	26 (23.0)	4 (12.9)	-
	Cytoreductive therapy (n = 276)				
	None (n = 51)	Hydroxycarbamide (n = 84)	Anthracyclines or cytarabine (n = 110)	Etoposide (n = 31)	*P*
CR*, n (%)	51 (100.0)	84 (100.0)	110 (100.0)	31 (100.0)	-
Time to CR, days, median (range)	37 (30-41)	38 (28-37)	36 (29-49)	35 (33-39)	0.393
PML-RARA ≥6.5% at end of induction	14 (27.5)	22 (26.2)	17 (15.5)	0 (0.0)	0.003
	Cytoreductive therapy (n = 267)				
	None (n = 51)	Hydroxycarbamide (n = 79)	Anthracyclines or cytarabine (n = 106)	Etoposide (n = 31)	*P*
CMR‡	50 (98.0)	78 (98.7)	106 (100.0)	31 (100.0)	0.508
2-year cumulative relapse (%)	3.962	8.861	1.887	0.000	0.040
Time to relapse†, months, median (range)	24.4 (17.1-36.7)	19.8 (6.2-52.9)	14.3 (10.1, 18.4)	-	-
Follow-up time, months, median (range)	64.0 (17.0-102.0)	68.0 (6.2-101.0)	57.0 (10.0-100.0)	17.0 (9.0-24.0)	-

* CR after induction therapy;
‡ CMR after the fourth rounds of consolidation therapy.
† The time to hematological/molecular/extramedullary relapse after a hematological CR.
ED, early death; CR, complete remission; CMR, complete molecular remission; *PML-RARA*, promyelocytic leukemia retinoic acid receptor alpha.

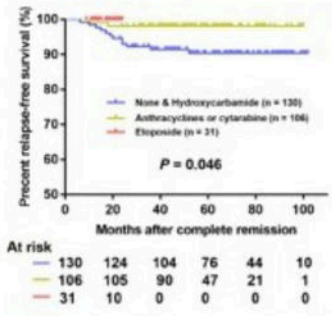

Figure 1. Kaplan-Meier plot of relapse-free survival (RFS) among no cytoreduction, hydroxycarbamide, anthracyclines/cytarabine and etoposide cytoreduction groups during induction therapy.

Figure 1

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