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POSTER ABSTRACTS

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

Cladribine Combined with Homoharringtonine and Cytarabine Achieves a High Remission Rate in Adult Patients with De Novo Acute Myeloid Leukemia, Especially for Adverse-Risk Group: A Prospective, Single Center, Single-Arm, Phase 2 Study

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Background: For adult de novo acute myeloid leukemia (AML), the standard 3+7 induction regimen has approximately 60% complete remission (CR) rate. Recently, BCL-2 inhibitor plus intensive chemotherapies as novel induction regimens have shown an above 90% composite complete remission (CRc) rate, however still have limited response effect in an adverse risk group, especially for patients with specific cytogenetic abnormalities such as KMT2A rearrangements, FLT3, RAS, and TP53 mutations. Multiple studies have shown that homoharringtonine (HHT) can target leukemia diseases that have switched their anti-apoptotic dependence from BCL-2 to MCL-1. We recently demonstrated that cladribine (CdA) could eradicate BCL-2 inhibitor-resistant monocytic leukemia stem cells driven by RAS mutants and KMT2A rearrangements. (Pei S, et al. Cancer Discovery. 2023) Together, these clinical and basic findings suggest a rationale for combining CdA with HHT to treat AML patients. In this study, we report the efficacy and safety of a newly designed "CHA" regimen composed of CdA, HHT, and cytarabine (AraC) in adult patients with de novo AML.
Methods: This is a prospective, single-center, single-arm phase 2 trial. Newly diagnosed AML patients aged 18-59 years were enrolled. The diagnosis, risk classification, and response evaluation were determined according to ELN 2022 criteria. All enrolled patients received the CHA regimen: CdA (5mg/m2, days 1-3), HHT (2mg/m2, days 1-5), and AraC (100mg/ m2, days 1-7) administered intravenously. The response was evaluated on day 28 via bone marrow routine and minimal residual disease (MRD) measurement by flow cytometry. The primary endpoint was CRc (CR plus CRi). Secondary endpoints were MRD, overall survival (OS), disease-free survival (DFS), event-free survival (EFS), and adverse events. Bone marrow (BM) samples on day 1 and 7 and peripheral blood (PB) samples on days 1-7 were collected for laboratory flow analysis to monitor the kinetics of leukemia reduction. We also treated primary AML specimens with single, dual, and triple combinations of CdA, HHT, and Ara-C to evaluate their anti-leukemic activity in vitro. Statistical analyses were carried out using SPSS 24.0. Survival curves were prepared using the Kaplan-Meier method. A two-tailed P value <0.05 was considered statistically significant. This trial is registered on ClinicalTrials.gov (NCT05906914).
Results: A total of 33 patients were enrolled from August 1, 2021, to April 15, 2023. The median age was 49 years. 33% (11/33) of patients were at favorable risk, 42% (14/33) were at intermediate risk, and 24% (8/24) were at adverse risk. After one course of CHA induction therapy, the CRc rate was 87% (27 of 31 patients), and the CR rate was 84% (26 of 31 patients). The CR

rates in the favorable, intermediate, and adverse-risk groups were 82% (9 of 11 patients), 75% (9 of 12 patients), and 100% (8 of 8 patients), respectively. Notably, six out of six patients with KMT2A rearrangement and ten out of ten patients with RAS mutations achieved MRD-negative CR. The overall MRD negativity was 89% (24 of 27 patients with CRc). In 31 evaluable patients, four patients did not reach CR; three of them held FLT3 mutations. 30-days treatment-related mortality (TRM) was 6% (2 of 33 patients), and both died of sepsis. The median neutrophil recovery time (from the end of chemotherapy to the neutrophil counts $\geq 0.5\times 109/L$) and platelets recovery time (from the end of chemotherapy to platelets counts $\geq 20\times 109/L$) were both 11 days. With a median follow-up time of 13 months (IQR: 6-17 months), the one-year OS was 86%, 1-year DFS was 89%, and the 1-year EFS was 76%. Flow cytometry analysis of serially collected PB and BM samples from nine randomly selected patients revealed that an average of 91.0% and 94.7% of leukemia burden was cleared in the PB and BM by day 7, respectively, demonstrating a rapid and effective response induced by CHA. Finally, our in vitro assay demonstrated a synergistic effect of CdA, HHT, and Ara-C on primary AML specimens including three patients with adverse-risk.

Conclusion: We propose the CHA regimen as a novel, effective, and safe chemotherapy regimen for newly diagnosed adult AML patients with remarkable potency in treating adverse-risk group patients, especially those with KMT2A rearrangements and RAS mutations that are otherwise resistant to BCL-2 inhibitor-based therapies, but a limited effect on FLT3mutated AML patients.

Disclosures No relevant conflicts of interest to declare.

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Table: Response assessment

	Overall (n=33)	Favorable risk (n=11)	Intermediate risk (n=14)	Adverse risk (n=8)
Response				
ORR	31/31 (100%)	11/11 (100%)	12/12 (100%)	8/8 (100%)
CRc	27/31 (87%)	10/11 (91%)	9/12 (75%)	8/8 (100%)
CR	26/31 (84%)	9/11 (82%)	9/12 (75%)	8/8 (100%)
CRi	1/31 (3%)	1/11(9%)	0	0
PR	4/31 (13%)	1/11(9%)	3/12 (25%)	0
NR	0	0	0	0
MRD negative[a]	24/27 (89%)	10/10 (100%)	7/9 (78%)	7/8 (88%)
Treatment-related mortality[b]	2/33 (6%)	0	2/14 (14%)	0
Median days for peripheral blood cell recovery, days (IQR)[c]				
ANC ≥0.5×10⁹/L	11.0(9.0-13.0)	11.0(9.0-14.0)	11.0(9.3-12.8)	11.5(10.3-12.8)
PLT ≥20×10⁹/L	11.0(8.0-13.0)	11.0(10.0-13.0)	10.0(6.3-13.5)	9.0(5.3-11.0)
Overall survival, months	Not reached	Not reached	Not reached	Not reached
Disease-free survival, months	Not reached	Not reached	Not reached	Not reached
Event-free survival, months	Not reached	Not reached	7.9	Not reached
1-year OS (95%CI)	86%	100%	67%	100%
1-year EFS (95%CI)	76%	100%	43%	100%
1-year DFS (95%CI)	89%	100%	71%	100%
1-year CIR (95%CI)	8%	0	22%	0

[a]*MRD negative: refers to the proportion of patients who achieved CRc after the first cycle of induction therapy;*

[b]*Treatment-related mortality: defined as death within 30 days of chemotherapy;*

[c]*Peripheral blood cell recovery time defined as the time from the end of the first course of chemotherapy to an absolute neutrophil count (ANC) ≥0.5×10⁹/L (or platelet count ≥20×10⁹/L) for 3 consecutive days;*

Figure

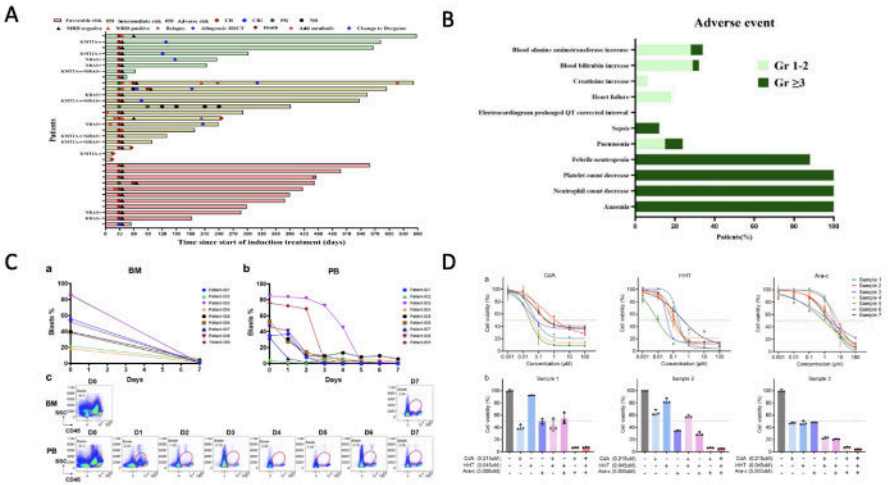

Figure: A. A swimmer plot of clinical response induced by CHA. Each bar represents an individual patient. B. The incidence of adverse events with two levels of grades: grade 1-2 and grade ⩾3. C. Flow cytometry analysis of serially collected PB and BM samples. a). A line graph showing the change of leukemia burden in the BM tissue of 9 *de novo* AML patients on day 0 and day 7. b). A line graph showing the change of leukemia burden in the serially collected PB tissue of 9 *de novo* AML patients between day 0 and day 7. c). Representative flow plots showing clearance of leukemia burden in patient 007 during 7 days of CHA treatment. AML blasts were indicated by red cycles, with blasts percentages shown. D. The CHA regimen potently eradicated primary AML specimens *in vitro*. a). Dose-response curves of seven primary AML specimens treated with increasing doses of CdA, HHT, and Ara-C for 48 hours. b). Viability of three adverse-risk AML patient specimens treated with CdA, HHT, and Ara-c alone or in combination. The dose of each drug was selected based on its corresponding clinical dose used in the CHA regimen. In A and B, data were presented as means ± SD, n = 3 technical replicates for each dose.

Figure 1