Homoharringtonine-based induction regimens for patients with de-novo acute myeloid leukaemia: a multicentre, open-label, randomised, controlled phase 3 trial

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Summary

Background Homoharringtonine-based induction regimens have been widely used in China for patients with acute myeloid leukaemia. However, their efficacy has not been tested in a multicentre randomised controlled trial in a large population. We assessed the efficacy and safety of homoharringtonine-based induction treatment for management of newly diagnosed acute myeloid leukaemia.

Methods This open-label, randomised, controlled, phase 3 study was done in 17 institutions in China between September, 2007, and July, 2011. Untreated patients aged 14–59 years with acute myeloid leukaemia were randomly assigned (by a computer-generated allocation schedule without stratification) to receive one of three induction regimens in a 1:1:1 ratio: homoharringtonine 2 mg/m² per day on days 1–7, cytarabine 100 mg/m² per day on days 1–7, and aclarubicin 20 mg/day on days 1–7 (HAA); homoharringtonine 2 mg/m² per day on days 1–7, cytarabine 100 mg/m² per day on days 1–7, and daunorubicin 40 mg/m² per day on days 1–3 (HAD); or daunorubicin 40–45 mg/m² per day on days 1–3 and cytarabine 100 mg/m² per day on days 1–7 (DA). Patients in complete remission were offered two cycles of intermediate-dose cytarabine (2 g/m² every 12 h on days 1–3). The primary endpoints were the proportion of patients who achieved complete remission after two cycles of induction treatment and event-free survival in the intention-to-treat population. The trial is registered in the Chinese Clinical Trial Register, number ChiCTR-TRC-06000054.

Findings We enrolled 620 patients, of whom 609 were included in the intention-to-treat analysis. 150 of 206 patients (73%) in the HAA group achieved complete remission versus 125 of 205 (61%) in the DA group (p=0·0108); 3-year event-free survival was 35·4% (95% CI 28·6–42·2) versus 23·1% (95% CI 17·4–29·3; p=0·0023). 133 of 198 patients (67%) in the HAD group had complete remission (*vs* DA, p=0·20) and 3-year event-free survival was 32·7% (95% CI 26·1–39·5; *vs* DA, p=0·08). Adverse events were much the same in all groups, except that more patients in the HAA (12 of 206 [5·8%]) and HAD (13 of 198 [6·6%]) groups died within 30 days than in the DA group (two of 205 [1%]; p=0·0067 *vs* HAA; p=0·0030 *vs* HAD).

Interpretation A regimen of homoharringtonine, cytarabine, and aclarubicin is a treatment option for young, newly diagnosed patients with acute myeloid leukaemia.

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Introduction

Acute myeloid leukaemia is common. In the USA, 13 780 cases are diagnosed per year, with an estimated 10 200 deaths.[1] The crude incidence of myeloid leukaemia in China is 2·57 cases per 100 000 people per year, with 1·25 deaths per 100 000 people per year.[2] Complete remission during induction chemotherapy prolongs survival. Daunorubicin and cytarabine is the gold standard for induction chemotherapy; however, it results in complete remission in only 50–75% of patients and 5-year overall survival is poor (9–23%).[3–5] Thus, a new treatment strategy is needed. The development of new induction treatments for patients with acute myeloid leukaemia has progressed little in the past four decades, with the exception of investigations of increased daunorubicin dose. In a study by Fernandez and colleagues,[6] daunorubicin 90 mg/m² improved the proportion of young patients who achieved a complete remission, and overall survival, compared with those receiving the standard dose of daunorubicin (45 mg/m²). Studies of induction using a three-drug combination have yielded controversial results that need to be further investigated. For example, addition of a third drug—eg, etoposide or tioguanine—to the induction regimen of daunorubicin and cytarabine does not confer an advantage,[7–9] but a report[10] from the Polish Adult Leukemia Group showed that addition of cladribine to the standard induction regimen could improve complete remission and overall survival.

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Homoharringtonine is an alkaloid derived from trees of the genus *Cephalotaxus* and has been used in China for treatment of acute and chronic myeloid leukaemia for more than 30 years. Its anti-leukaemic effects work primarily through inhibition of protein synthesis to induce differentiation, inhibit proliferation, and promote apoptosis of leukaemic cells.[11–14] It also affects leukaemia stem cells.[15] Moreover, homoharringtonine has been reported to have significant synergistic effects with cytarabine.[13]

We have shown that homoharringtonine combined with cytarabine and aclarubicin is well tolerated and efficacious.[16] 83% of newly diagnosed young patients with acute myeloid leukaemia achieved complete remission and estimated 3-year overall survival was 53%. Xiao and colleagues[17] showed that in young untreated patients, a regimen of homoharringtonine, cytarabine, and daunorubicin resulted in complete remission in 86·1% of patients, and a 3-year overall survival of 55·9%. However, the efficacy of such regimens has not been confirmed by multicentre randomised controlled trials in large populations. We assessed the efficacy and safety of homoharringtonine-based induction regimens for treatment of newly diagnosed acute myeloid leukaemia.

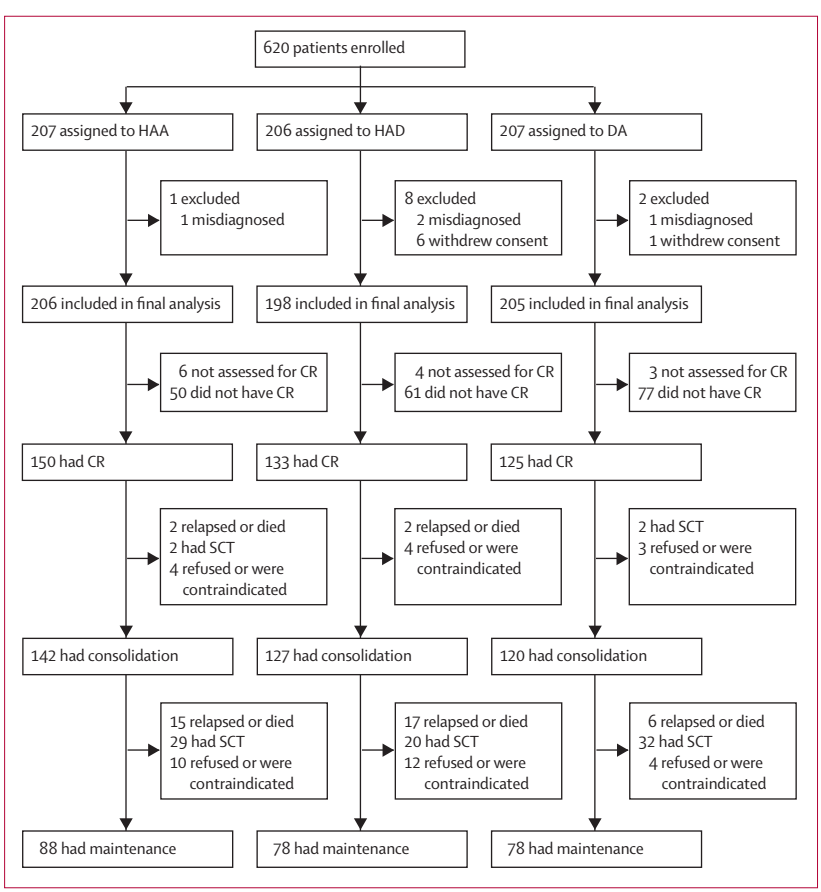

Figure 1: **Trial profile**
HAA=homoharringtonine, cytarabine, aclarubicin. HAD=homoharringtonine, cytarabine, daunorubicin. DA=daunorubicin, cytarabine. CR=complete remission. SCT=stem-cell transplantation.

Methods

Study design and participants

This study was a randomised, parallel, controlled, open-label, phase 3 trial done in 17 institutions in four regions of China (north China, south China, east China, and the Yangtze river valley). Inclusion criteria were: confirmed acute myeloid leukaemia according to WHO classification,[18] no previous treatment for acute myeloid leukaemia, age 14–59 years, WHO performance status of 2 or less, normal cardiac function (left ventricular ejection fraction ≥50%), adequate liver and renal function (serum bilirubin concentration ≤35 μmol/L, aspartate aminotransferase and alanine aminotransferase concentrations less than two times the upper limit of normal, serum creatinine concentration ≤150 μmol/L). We excluded patients who had acute promyelocytic leukaemia or acute myeloid leukaemia transformed from myelodysplastic syndrome, patients with other blood diseases, patients with tuberculosis or other cancers, patients who were pregnant (for women of childbearing age, β-subunit of human chorionic gonadotropin was tested) or breastfeeding, patients who were intolerant or allergic to any of the drugs used in the trial, and patients who could not understand or comply with the protocol.

The study was approved by the ethics committee of the Chinese Academy of Medical Science and done in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Randomisation and masking

We used a simple randomisation method without stratification to minimise investigator and participant bias. Each patient was assigned a serial number based on the sequence of enrolment by telephone call to the coordinating hospital. Then, a unique randomisation number was generated for each serial number and the randomisation numbers were sorted ascendingly. The first third of randomisation numbers were assigned to daunorubicin 40–45 mg/m² per day on days 1–3 and cytarabine 100 mg/m² per day on days 1–7 (DA). The middle third were assigned to homoharringtonine 2 mg/m² per day on days 1–7, cytarabine 100 mg/m² per day on days 1–7, and aclarubicin 20 mg/day on days 1–7 (HAA). The last third were assigned to homoharringtonine 2 mg/m² per day on days 1–7, cytarabine 100 mg/m² per day on days 1–7, and daunorubicin 40 mg/m² per day on days 1–3 (HAD). We generated the randomisation sequence with STATA (version 10.0). Investigators giving treatments and participants were not masked to treatment assignment, but those who assessed outcomes and analysed data were.

Procedures

Patients who had partial remission or had a decrease of blast cells of 60% or more were given a second course of the same induction regimen. In an interim analysis in April, 2009, we noted that the proportion of patients who achieved complete remission was low for those who were treated with the daunorubicin and cytarabine regimen compared with those who received the HAA regimen. Therefore, the DA regimen was modified, increasing the dose of daunorubicin from 40 mg/m² per day to 45 mg/m² per day on days 1–3.

Patients in complete remission were offered consolidation treatment of two cycles of intermediate-dose cytarabine (2 g/m², every 12 h on days 1–3). Patients with unfavourable cytogenetic risk were then recommended to have allogeneic haemopoietic stem-cell transplantation if they had an HLA-identical sibling or unrelated donor. Patients with favourable or intermediate cytogenetic risk were offered four cycles of one of four regimens: DA; homoharringtonine 2 mg/m² per day on days 1–7 and cytarabine 100 mg/m² per day on days 1–7; mitoxantrone 8 mg/m² per day on days 1–3 and cytarabine 100 mg/m² per day on days 1–7; or cytarabine 100 mg/m² day on days 1–7 and aclarubicin 20 mg/day on days 1–7.

Patients in complete remission were offered prophylactic treatment with four rounds of intrathecal administration of methotrexate 10 mg, cytarabine 50 mg, and dexamethasone 5 mg if CSF was continuous normal (chemical and cytopathology in the normal range); otherwise, intrathecal administration would be twice per week, until CSF became normal, then they would receive intrathecal administration monthly for another 4 months. CSF was tested each time a patient received prophylactic CNS treatment.

Adverse events were monitored with WHO score[19] and recorded in case report forms. During treatment, dose reductions or interruptions were permitted if the patients had drug-related grade 3–4 non-haematological toxic effects. At each site, investigators reminded the patients to come back to the hospital for chemotherapy as scheduled, and followed up patients every 3 months after treatment by telephone.

	HAA (n=206)	HAD (n=198)	DA (n=205)
Sex			
Male	111 (54%)	100 (51%)	105 (51%)
Female	95 (46%)	98 (49%)	100 (49%)
Mean age (SD; years)	36 (12)	37 (12)	38 (12)
Median white blood-cell count (IQR; 10^9/L)	15·9 (4·9–48·3)	13·1 (4·9–40·7)	17·9 (5·0–47·8)
Mean haemoglobin concentration (SD; g/L)	80 (22)	81 (22)	79 (22)
Median platelet count (IQR; 10^9/L)	39 (17–68)	37 (23–66)	36 (18–64)
FAB subtype			
M0	1 (<1%)	5 (3%)	1 (<1%)
M1	17 (8%)	12 (6%)	18 (9%)
M2	81 (39%)	73 (37%)	89 (43%)
M4	48 (23%)	35 (18%)	40 (20%)
M5	48 (23%)	66 (33%)	55 (27%)
M6	8 (4%)	3 (2%)	2 (1%)
Not established	3 (1%)	4 (2%)	0
Cytogenetic risk			
Favourable	37 (18%)	30 (15%)	39 (19%)
Intermediate	110 (53%)	101 (51%)	104 (51%)
Not favourable	20 (10%)	21 (11%)	17 (8%)
Unknown	39 (19%)	46 (23%)	45 (22%)
NPM1 status			
Mutated	24 (12%)	20 (10%)	20 (10%)
Wild-type	136 (66%)	133 (67%)	147 (72%)
Unknown	46 (22%)	45 (23%)	38 (19%)
FLT3 internal duplication status			
Positive	21 (10%)	19 (10%)	27 (13%)
Negative	148 (72%)	148 (75%)	151 (74%)
Unknown	37 (18%)	31 (16%)	27 (13%)
CEBPA status			
Mutated	23 (11%)	21 (11%)	30 (15%)
Wild-type	96 (47%)	99 (50%)	95 (46%)
Unknown	87 (42%)	78 (39%)	80 (39%)
Integrated risk			
Favourable	58 (28%)	44 (22%)	61 (30%)
Not favourable	71 (34%)	75 (38%)	63 (31%)
Unknown	77 (37%)	79 (40%)	81 (40%)
Region			
North China	54 (26%)	60 (30%)	63 (31%)
South China	50 (24%)	46 (23%)	46 (22%)
East China	38 (18%)	41 (21%)	44 (21%)
Yangtze river valley	64 (31%)	51 (26%)	52 (25%)

Data are n (%) unless otherwise stated. HAA=homoharringtonine, cytarabine, aclarubicin. HAD=homoharringtonine, cytarabine, daunorubicin. DA=daunorubicin, cytarabine. FAB=French–American–British.

Table 1: **Baseline characteristics**

	DA (n=205)	HAA (n=206)		HAD (n=198)	
	n/N (%)	n/N (%)	p value*	n/N (%)	p value*
Complete remission after one cycle	109/205 (53%)	135/206 (66%)	0·0107	126/198 (64%)	0·0331
Favourable cytogenetics	25/39 (64%)	33/37 (89%)	0·0101	22/30 (73%)	0·41
Intermediate cytogenetics	55/104 (53%)	74/110 (67%)	0·0316	65/101 (64%)	0·10
Unfavourable cytogenetics	7/17 (41%)	9/20 (45%)	0·82	10/21 (48%)	0·69
Unknown cytogenetics	22/45 (49%)	19/39 (49%)	0·99	29/46 (63%)	0·17
Overall complete remission†	125/205 (61%)	150/206 (73%)	0·0108	133/198 (67%)	0·20
Favourable cytogenetics	27/39 (69%)	35/37 (95%)	0·0044	23/30 (77%)	0·49
Intermediate cytogenetics	64/104 (62%)	83/110 (75%)	0·0282	67/101 (66%)	0·47
Unfavourable cytogenetics	7/17 (41%)	9/20 (45%)	0·82	10/21 (48%)	0·69
Unknown cytogenetics	27/45 (60%)	23/39 (59%)	0·92	33/46 (72%)	0·24

HAA=homoharringtonine, cytarabine, aclarubicin. HAD=homoharringtonine, cytarabine, daunorubicin. DA=daunorubicin, cytarabine. *Compared with DA. †Complete response after two cycles of induction treatment.

Table 2: **Complete remissions with each induction treatment**

	DA (n=205)	HAA (n=206)	p value (HAA *vs* DA)	HAD (n=198)	p value (HAD *vs* DA)
Overall					
Event-free survival					
Events	154/205 (75%)	127/206 (62%)	..	130/198 (66%)	..
Median time (95% CI; months)	6·9 (4·0–9·8)	11·7 (8·6–14·8)	..	8·6 (5·4–11·8)	..
At 3 years (95% CI)	23·1% (17·4–29·3)	35·4% (28·6–42·2)	0·0023	32·7% (26·1–39·5)	0·08
Overall survival					
Deaths	114/205 (56%)	106/206 (51%)	..	103/198 (52%)	..
Median time (95% CI; months)	21·1 (15·1–27·1)	26·0 (16·3–35·7)	..	22·6 (12·3–32·9)	..
At 3 years (95% CI)	42·7% (35·5–49·7)	44·5% (37·1–51·6)	0·53	43·5% (35·8–50·9)	0·92
Relapse-free survival					
Relapses or deaths	74/125 (59%)	71/150 (47%)	..	66/133 (50%)	..
Median time (95% CI; months)	15·5 (10·8–20·2)	31·3 (14·1–not reached)	..	21·7 (13·8–not reached)	..
At 3 years (95% CI)	37·9% (29·0–46·7)	48·8% (40·1–56·9)	0·09	46·3% (36·9–55·1)	0·19
Favourable and intermediate cytogenetics					
Event-free survival					
Events	106/143 (74%)	78/147 (53%)	..	87/131 (66%)	..
Median time (95% CI; months)	7·6 (5·2–10·0)	15·2 (5·0–25·4)	..	8·0 (4·7–11·3)	..
At 3 years (95% CI)	24·0% (17·1–31·6)	44·7% (36·3–52·7)	0·0001	30·9% (22·9–39·2)	0·36
Overall survival					
Deaths	85/143 (59%)	65/147 (44%)	..	69/131 (53%)	..
Median time (95% CI; months)	19·8 (13·9–25·7)	Not reached	..	20·6 (8·8–32·4)	..
At 3 years (95% CI)	39·8% (31·3–48·1)	52·1% (43·2–60·3)	0·0175	42·1% (32·7–51·2)	0·87
Relapse-free survival					
Relapses or deaths	54/91 (59%)	49/118 (42%)	..	47/90 (52%)	..
Median time (95% CI; months)	15·9 (9·6–22·2)	Not reached	..	17·7 (8·4–27·0)	..
At 3 years (95% CI)	37·8% (27·4–48·1)	55·8% (46·0–64·5)	0·0181	43·9% (33·0–54·3)	0·60
Unfavourable cytogenetics					
Event-free survival					
Events	12/17 (71%)	19/20 (95%)	..	15/21 (71%)	..
Median time (95% CI; months)	1·2 (0·7–1·7)	2·4 (1·5–3·3)	..	2·1 (0·0–11·9)	..
At 3 years (95% CI)	29·4% (10·7–51·2)	NA*	0·46	28·6% (11·7–48·2)	1·00
Overall survival					
Deaths	10/17 (59%)	18/20 (90%)	..	12/21 (57%)	..
Median time (95% CI; months)	11·8 (7·4–16·2)	6·9 (1·2–12·6)	..	13·4 (2·6–24·2)	..
At 3 years (95% CI)	41·2% (18·6–62·6)	7·5% (0·6–26·6)	0·07	38·4% (17·6–59·0)	0·99
Relapse-free survival					
Relapses or deaths	2/7 (29%)	8/9 (89%)	..	4/10 (40%)	..
Median time (95% CI; months)	Not reached	5·5 (0·5–10·5)	..	Not reached	..
At 3 years (95% CI)	71·4% (25·8–92·0)	NA*	0·07	60·0% (25·3–82·7)	0·83

Data are n/N (%), median (95% CI), or % estimate (95% CI) unless otherwise stated. NA=not available. HAA=homoharringtonine, cytarabine, aclarubicin. HAD=homoharringtonine, cytarabine, daunorubicin. DA=daunorubicin, cytarabine. *No patients survived longer than 3 years without events or relapse.

***Table 3*: Survival results**

We classified cytogenetic risk according to the modified Southwest Oncology Group criteria:[20] (1) favourable risk, including t(8;21) and inv(16) or t(16;16)(p13;q22); (2) unfavourable risk, including del(5q) or monosomy 5, monosomy 7 or del(7q), abnormal 3q, 9q, 11q, 21q, or 17p, t(6;9), t(9;22), and complex karyotypes (≥3 unrelated chromosomes abnormal); and (3) intermediate risk, including normal karyotypes and all other anomalies. We tested for mutations in the *NPM1* and *CEBPA*, and for *FLT3* internal tandem duplication centrally in the First Affiliated Hospital (Zhejiang University College of Medicine); favourable genotypes were defined as a normal karyotype and *NPM1*, but not *FLT3* internal tandem duplication or a normal karyotype with *CEBPA* mutation.[21] Patients with favourable cytogenetics and favourable genotype were classed as having favourable integrated risk.

The primary endpoints were the proportion of patients who had overall complete remission after two

cycles of induction treatment and event-free survival. Complete remission was defined as less than 5% blast cells in normocellular bone marrow, peripheral blood counts showing at least 1×10^9 neutrophils per L and at least 100×10^9 platelets per L, and the disappearance of all clinical signs of leukaemia. Event-free survival was defined as the time from randomisation to assessment of response after the last induction cycle if the patient was not in complete remission, the date of relapse, or the date of death, whichever came first. The secondary endpoints were overall and relapse-free survival. Overall survival was measured from randomisation to the date of death from any cause. Relapse-free survival was measured from the time of complete remission to the date of relapse or the date of death.

Early death was defined as death within 30 days of randomisation. The duration of neutropenia and thrombocytopenia was analysed in patients who achieved complete remission and defined as the time from start of induction treatment to the last day on which neutrophil count was less than $0\cdot5\times10^9$ neutrophils per L and platelet count was less than 50×10^9 platelets per L.

Statistical analysis

We compared each experimental group (HAA and HAD) with the control group (DA) for the intention-to-treat populations (with a significance threshold of 0·05). The sample size was chosen to detect an increase of 3-year event-free survival from 23% in the control group to 35% in the experimental groups and a hazard

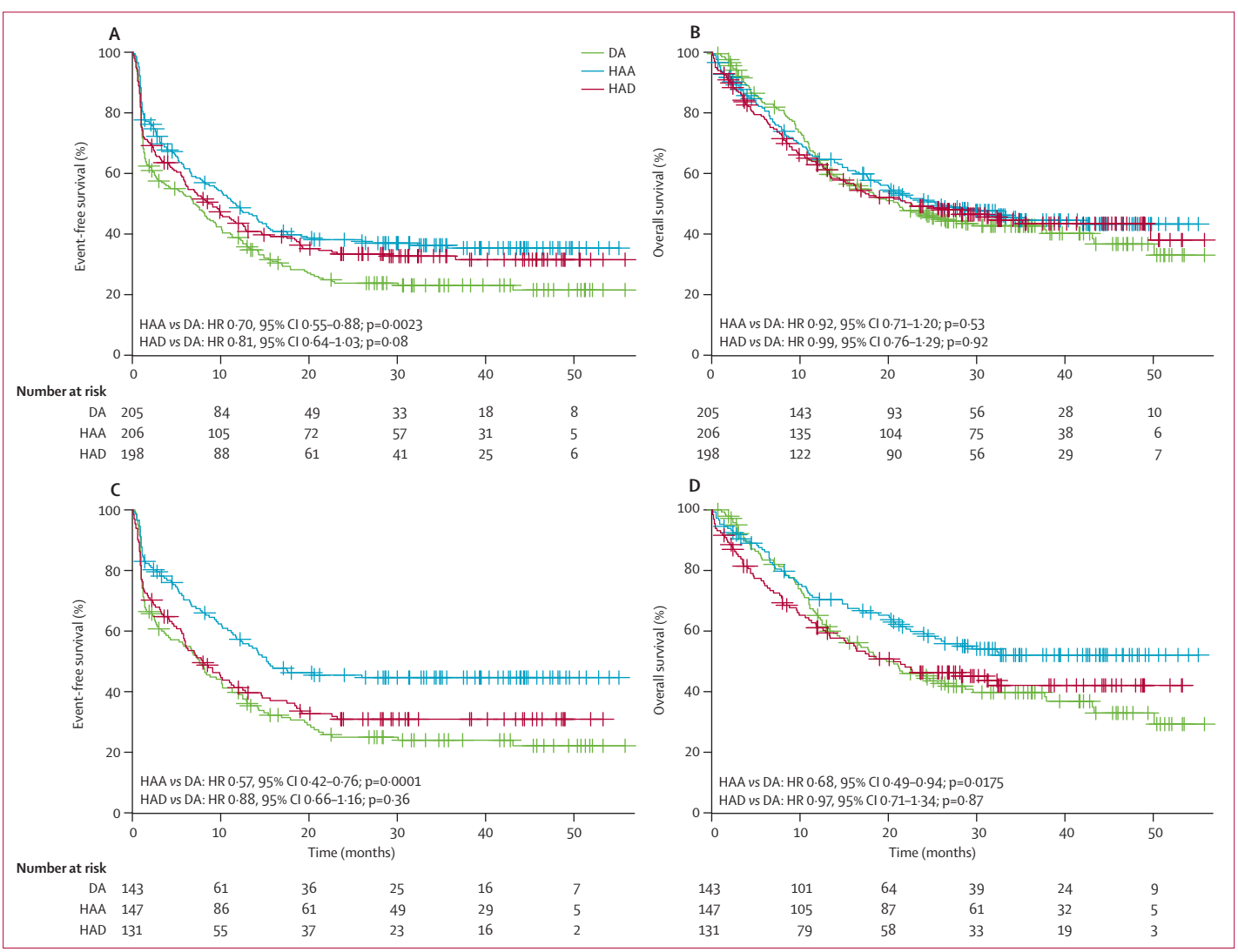

Figure 2: **Kaplan-Meier curves of survival with different induction treatments**
Event-free survival of all patients (A) and patients with a favourable and intermediate cytogenetic profile (C), and overall survival of all patients (B) and patients with a favourable and intermediate cytogenetic profile (D). HAA=homoharringtonine, cytarabine, aclarubicin. HAD=homoharringtonine, cytarabine, daunorubicin. DA=daunorubicin, cytarabine. HR=hazard ratio.

ratio (HR) of 0·70. With a type I error rate of 0·05 and 80% power, 200 patients per study group and a total of 359 events were needed. This sample size also provided adequate power to detect differences in complete remission.

For analyses of complete remission, missing data were imputed as no complete remission; for survival analyses, missing data were imputed as censored. Complete remission was compared with the χ^2 test or Fisher's exact test. The treatment effect and other covariates for complete remission were analysed by logistic regression. All survival endpoints were estimated with the Kaplan-Meier method and compared by log-rank tests with HRs estimated by the Cox model, and checked for proportional hazard assumptions with R (version 2.14.0).[22] We used the Breslow-Day χ^2 test to assess homogeneity of outcome by regions. Regional effects and interaction of regions and treatment groups were also assessed by multivariate analyses. The assessment of effects of treatment in subgroups was post-hoc. All tests were two-tailed. Statistical analyses were done with SPSS (version 19.0), STATA (version 11.0), and R (version 2.14.0).

This study is registered with the Chinese Clinical Trial Register, number ChiCTR-TRC-06000054.

Role of the funding source

The sponsor had no role in study design, collection, analysis, or interpretation of data, or writing the report. All the authors had access to the raw data. The corresponding authors had the final responsibility for the decision to submit for publication.

Results

We enrolled 620 patients between September, 2007, and July, 2011. 11 were ineligible because of incorrect diagnosis or withdrawal of informed consent (figure 1); therefore, we included 609 patients in the analysis. Mean age was 37 years (SD 12). Median follow-up was 17·5 months (IQR 6·6–32·8) overall, and was 32·7 months (25·6–43·5) in survivors. 50 of 609 patients (8%) were lost to follow-up. Baseline characteristics did not differ substantially between groups (table 1). We had cytogenetic data for 479 patients (79%); adequate metaphase cells could not be obtained from the other patients. 480 patients were screened for mutations in *NPM1*, 514 for *FLT3* internal tandem duplication, and 364 for mutations in *CEBPA*; 57 patients with a normal karyotype were classified as favourable genotype subgroup according to their mutation status.

Of 609 patients, 370 (61%) had complete remission after the first course of induction treatment. Fewer patients had complete remission after one cycle in the DA group than in the HAA group and HAD group (table 2). Of the 54 patients who received the second repeated induction treatment, 15 of 19 (79%) in the HAA group, seven of 13 (54%) in the HAD group, and 16 of 22 (73%) in the DA group achieved complete remission. Overall complete remission was significantly more common in the HAA group than in the DA group (150 of 206 [73%] *vs* 125 of 205 [61%]; p=0·0108), particularly in patients with favourable and intermediate cytogenetics (table 2). In the HAD group, 133 of 198 (67%) patients had complete remission (*vs* DA, p=0·20). In multivariate analyses, we noted no significant difference between regions (p=0·17) or interaction between regions and treatment groups (p=0·80). After adjustment for region, age, and cytogenetic risk, the odds ratio of complete remission for HAA versus DA was 1·72 (95% CI 1·12–2·64; p=0·0131) and for HAD versus DA, it was 1·34 (0·88–2·04; p=0·17). The proportion of patients who achieved complete remission did not differ significantly between regions (HAA *vs* DA p=0·55; HAD *vs* DA p=0·88; by Breslow-Day χ^2 test).

389 (95%) of 408 patients who achieved complete remission received consolidation treatment, with much

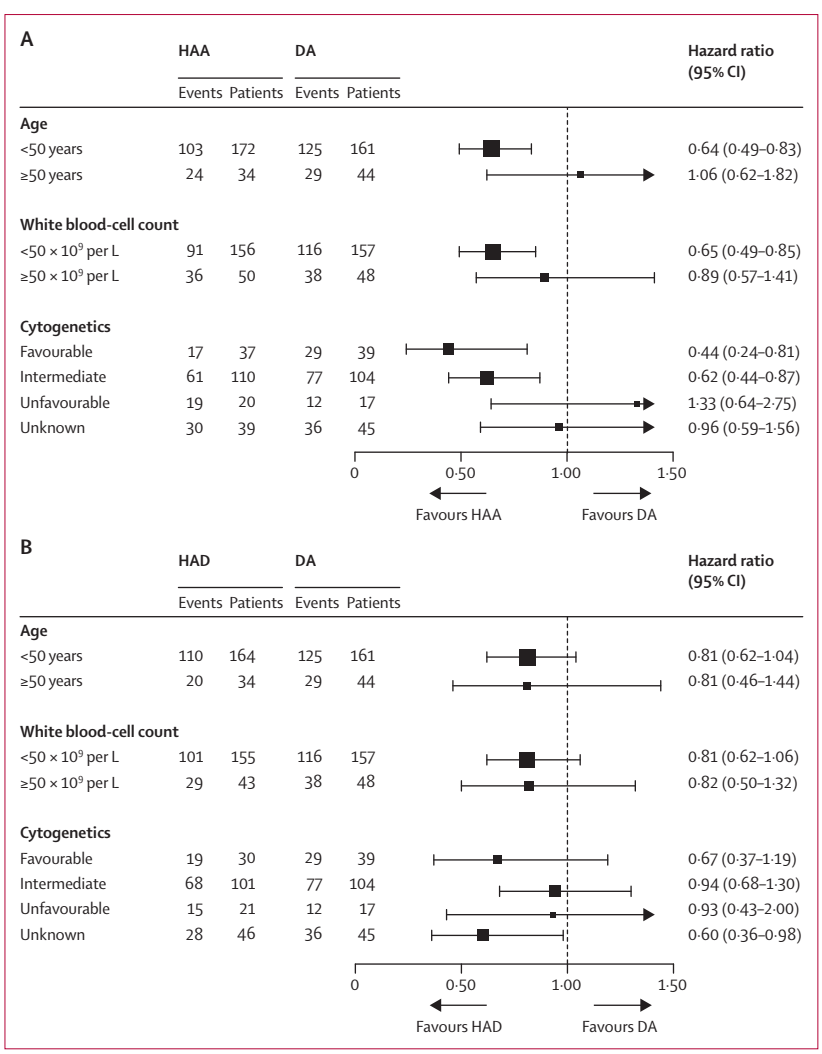

Figure 3: **Hazard ratios for event-free survival by subgroup**
(A) HAA versus DA, (B) HAD versus DA. Estimated with a univariate Cox model. HAA=homoharringtonine, cytarabine, aclarubicin. HAD=homoharringtonine, cytarabine, daunorubicin. DA=daunorubicin, cytarabine.

the same proportion in each group receiving such therapy (figure 1). Maintenance treatment was 244 (63%) of 389 patients, again well balanced across groups. Overall, 85 patients received allogeneic hemopoietic stem-cell transplantation (31 [15%] of 206 in the HAA group, 20 [10%] of 198 in the HAD group, and 34 [17%] of 205 in the DA group).

3-year event-free survival was significantly higher in the HAA group (35·4%, 95% CI 28·6–42·2) than in the DA group (23·1%, 95% CI 17·4–29·3%; p=0·0023; table 3, figure 2A). 3-year event-free survival in the HAD group was 32·7% (95% CI 26·1–39·5; *vs* DA p=0·08; table 3, figure 2A). In multivariate analyses, we noted no regional effect (p=0·30), and the interaction between regions and treatment groups was not significant (p=0·73). After adjustment for region, white blood-cell count, haemoglobin concentration, and cytogenetic risk, the HR of events for HAA versus DA was 0·71 (95% CI 0·56–0·89; p=0·0039) and for HAD versus DA it was 0·81 (0·64–1·02; p=0·07). The difference between HAA and DA groups was still significant after the patients who underwent allogeneic hemopoietic stem-cell transplantation in complete remission were censored at the day of transplantation (HR 0·72, 95% CI 0·57–0·92; p=0·0083). In subgroup analysis, event-free survival in patients taking HAA was greatest for those with favourable prognostic factors—eg, being younger than 50 years, white blood-cell count less than 50×10^9 per L, and favourable or intermediate cytogenetics (figure 3). No prognostic factors were significant for the comparison between HAD and DA groups (figure 3).

Overall and relapse-free survival did not differ significantly between groups (table 3, figure 2B, appendix). In a subgroup analysis, patients with favourable and intermediate cytogenetics in the HAA group had better overall survival and relapse-free survival than those in the DA group (table 3, figure 2D, appendix). In multivariate analyses, after adjustment for prognostic covariates, the HR for death in the HAA group versus DA group was 0·68 (95% CI 0·49–0·95; p=0·0213) and the HR for relapse or death in the HAA versus DA group was 0·59 (0·40–0·87; p=0·0080). Overall survival and relapse-free survival in patients with favourable and intermediate cytogenetics did not differ significantly between the HAD and DA groups (table 3, figure 2D, appendix). Overall and relapse-free survival did not differ significantly between treatment groups in patients with unfavourable cytogenetics (table 3).

57 patients were classified as having a favourable genotype with normal karyotype. In patients with favourable integrated risk, both the HAA and HAD regimens improved event-free survival compared with the DA regimen (for HAA, HR 0·38, 95% CI 0·23–0·61; p=0·0001; for HAD, HR 0·60, 95% CI 0·37–0·97; p=0·0362). Relapse-free survival in these patients was better with the HAA regimen compared with the DA regimen (HR 0·44, 95% CI 0·25–0·78; p=0·0051); for the HAD versus DA group the HR was 0·55 (95% CI 0·30–1·01; p=0·05). Overall survival did not differ significantly between treatment groups. For patients in the non-favourable group, the three treatment groups did not differ significantly (figure 4).

Non-haematological and haematological toxic effects did not differ significantly between groups (table 4). Six patients needed dose reduction during induction treatment—of whom four were in the HAD group and two were in the DA group—because of possibly drug-related grade 3–4 non-haematological effects, including cardiac toxic effects, liver dysfunction, or serious infection with grade 4 neutropenia. 13 patients had to discontinue induction treatment, of whom three were in the HAA group, seven were in the HAD group, and three

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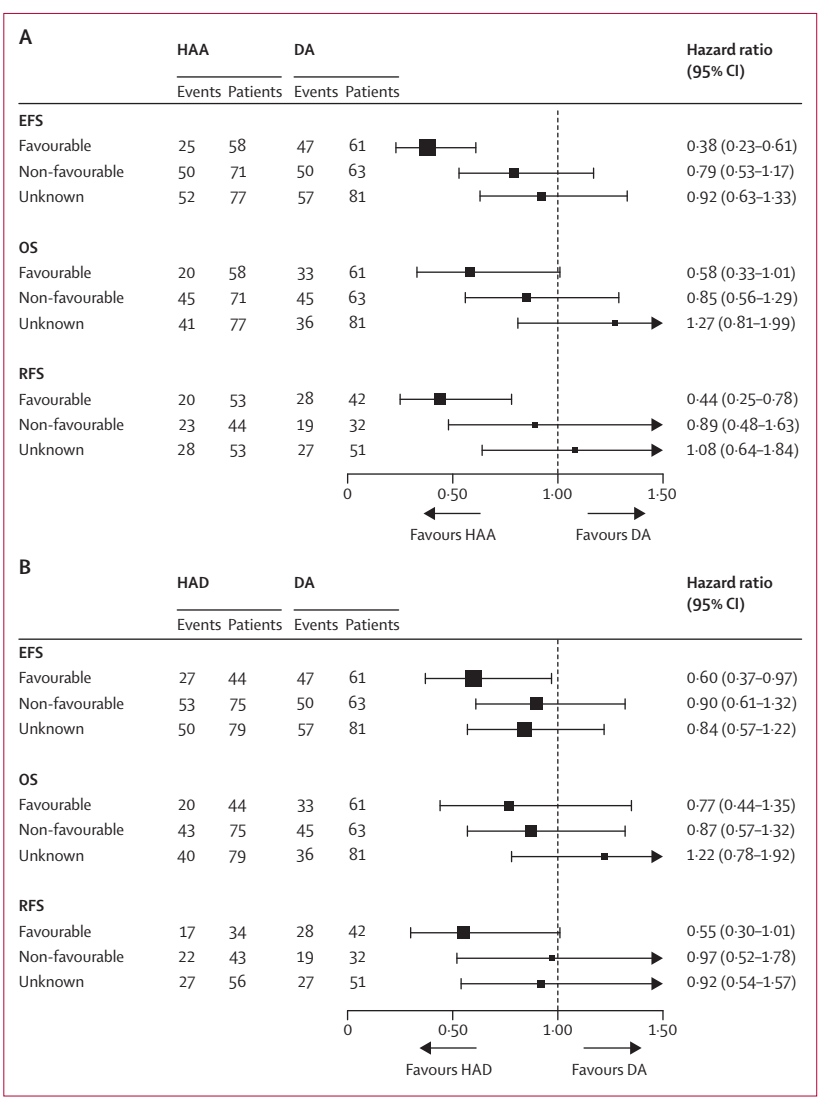

Figure 4: **Hazard ratios for event-free survival, recurrence-free survival, and overall survival according to genotype and cytogenetics**

(A) HAA versus DA, (B) HAD versus DA. Patients with favourable genotype and favourable cytogenetics were classed as favourable. Estimated with a univariate Cox model. HAA=homoharringtonine, cytarabine, aclarubicin. HAD=homoharringtonine, cytarabine, daunorubicin. DA=daunorubicin, cytarabine. OS=overall survival. EFS=event-free survival. RFS=relapse-free survival.

	HAA (n=206)	HAD (n=198)	DA (n=205)	p value
Grade 3–4				
Haemorrhage	10/191 (5%)	15/186 (8%)	13/193 (7%)	0·55
Hepatic	5/189 (3%)	4/185 (2%)	3/192 (2%)	0·77
Renal	0/187	0/183	0/193	..
Cardiac	3/188 (2%)	3/185 (2%)	0/193	0·20
Gastrointestinal	12/182 (7%)	11/172 (6%)	9/184 (5%)	0·75
Infectious (grade 1–4)	156/188 (83%)	141/178 (79%)	144/186 (77%)	0·39
Median duration of neutropenia (IQR; days)	15 (12–18)	16 (13–19)	18 (13–21)	0·31
Median duration of thrombocytopenia (IQR; days)	20 (17–22)	19 (16–21)	19 (16–22)	0·36

Data are n (%) or n/N (%) unless otherwise stated. Data for haematological toxic effects (neutropenia and thrombocytopenia) includes only the patients who had complete response after one cycle of induction treatment. Neutropenia defined as $<0{\cdot}5 \times 10^9$ cells per L. Thrombocytopenia defined as $<50 \times 10^9$ cells per L.

Table 4: **Toxic effects during induction treatment**

were in the DA group. Reasons for discontinuation were coma, cardiac toxic effects, and gastrointestinal bleeding. More patients died early (within 30 days of randomisation) in the HAA group (n=12, 5·8%; p=0·0067) and HAD group (n=13, 6·6%; p=0·0030) compared with the DA group (n=2, 1%). Causes of death were infection (n=10), pulmonary failure (n=4), haemorrhage (n=10), tumour lysis syndrome (n=1), and intestinal obstruction (n=2). Of the patients who had dose reduction or discontinuation, only one (who had a mental disorder caused by tumour lysis syndrome) died early.

Discussion

Our study is, to the best of our knowledge, the first randomised, multicentre, controlled, phase 3 trial in China to compare the efficacy and safety of homoharringtonine-based induction regimens with a DA regimen in young untreated patients with acute myeloid leukaemia. The HAA regimen resulted in a significantly more complete remissions and improved event-free survival compared with DA. More patients with favourable and intermediate cytogenetics who took HAA achieved complete remission, and these patients had longer event-free survival, than those who took DA. These results suggest that an HAA induction regimen is a treatment option for patients with acute myeloid leukaemia, especially for those with favourable and intermediate cytogenetics. By contrast, overall complete remission and event-free survival did not differ significantly between the HAD and DA groups.

The overall proportion of patients who achieved a complete remission in the HAA group was 12% higher than in the DA group. This improvement is similar to that previously reported with high-dose daunorubicin (270 mg/m²) induction treatment, in which the proportion of patients who achieved a complete remission was 10·5–13·3% higher than with the standard DA treatment.[6,23] The benefit of HAA on complete remission was mainly in patients with favourable cytogenetics, of whom 95% had complete remission. Overall complete remission in patients receiving HAA in our study was similar to that in another study[24] in which patients received another intensive daunorubicin regimen (250 mg/m²; 77·5%) or a standard dose of idarubicin (78·2%). In patients with favourable cytogenetic risk, complete remission in the HAA group (95%) was also similar to the intensive daunorubicin regimen (96%) and standard-dose idarubicin regimen (91%).

Patients in the HAA group had better event-free survival than did those in the DA group. This difference was mainly a consequence of improved outcome in patients with favourable and intermediate cytogenetics. The HAA regimen improved overall survival and relapse-free survival compared with DA for patients with low and intermediate cytogenetic risk. However—as with intensive chemotherapy[6,23]—the HAA regimen did not benefit patients with unfavourable risk. Therefore, a new treatment approach is needed to improve the outcome of patients with high-risk acute myeloid leukaemia.

Addition of homoharringtonine to induction treatment mainly benefited patients in the HAA group rather than those in the HAD group. Previous studies[7–10] have shown that three-drug combination chemotherapy does not provide a substantial benefit to patients with acute myeloid leukaemia. Therefore, we believe that the advantage of the addition of homoharringtonine might be related to the synergistic effects of homoharringtonine and aclarubicin rather than intensified chemotherapy. In-vitro studies[25] show that homoharringtonine and aclarubicin can inhibit the growth and induce apoptosis of leukaemia cell lines and primary cells through down-regulation of the PI3K-AKT and WNT pathways, respectively. Furthermore, in vivo, homoharringtonine combined with aclarubicin inhibits tumour growth and prolongs survival in a mouse model of acute myeloid leukaemia.[25]

Of note, the three-drug combination increased early death compared with DA. Infection and haemorrhage were the two main causes of early death. However, early deaths in the HAA or HAD groups was similar to that in patients given high-dose daunorubicin (5·5%).[6] Early deaths were also less common in groups given HAA or HAD than in those who received other three-drug combination chemotherapy regimens—eg, daunorubicin, cytarabine, and cladribine, or daunorubicin, cytarabine, and fludarabine—in which 10–11% of patients died during hypoplasia induced by induction treatment.[10]

Our study has several limitations. The dose of daunorubicin in the control group was 40–45 mg/m² per day for 3 days, which is the standard dose according to the Leukemia Study Group of Hematology Branch of the Chinese Medical Association.[26] This dose is lower than the dose (60 mg/m² per day for 3 days) used in other studies in western countries.[27] However, complete remission was similar across studies, even with intensive daunorubicin. Fernandez and colleagues[6] reported complete remission

***Panel:* Research in context**

Systematic review

We searched PubMed with the terms "homoharringtonine" and "acute myeloid leukemia" for studies of homoharringtonine in patients with acute myeloid leukaemia up to Jan 1, 2013. We restricted our search to publications in English. We excluded studies of children or elderly patients. Homoharringtonine or homoharringtonine-based chemotherapy was often investigated for patients with relapsed or refractory acute myeloid leukaemia, or acute myeloid leukaemia transformed from myelodysplastic syndrome.[28–31] Only three non-parallel controlled studies[16,17,32] assessed homoharringtonine-based chemotherapy for untreated young patients with acute myeloid leukaemia, which showed that these regimens were efficacious and safe. In one study,[16] 83% of patients treated with homoharringtonine in combination with cytarabine and aclarubicin had a complete response and 53% were still alive after 3 years. In another study,[17] 86% had a complete response, 3-year disease-free survival was 46% and 3-year overall survival was 56%. Mi and colleagues[32] also reported that homoharringtonine combined with cytarabine and aclarubicin or mitoxantrone had improved complete response and survival. We did not find any randomised prospective studies of homoharringtonine-based chemotherapy for untreated young patients with acute myeloid leukaemia.

Interpretation

Our results further support that an induction regimen of homoharringtonine, cytarabine, and aclarubicin prolongs event-free survival and increases the proportion of patients who achieve a complete remission compared with daunorubicin and cytarabine. The regimen also seems to increase overall survival and recurrence-free survival in patients with favourable and intermediate cytogenetics. Our work suggests that the homoharringtonine, cytarabine, and aclarubicin regimen could be used as a new front-line treatment for low-risk and intermediate-risk patients with acute myeloid leukaemia.

in 57·3% of patients taking daunorubicin 45mg/m², whereas Holowiecki and coworkers[10] reported complete remission in 56% of patients taking 60 mg/m². 3-year overall survival in our control group was 42·7%, compared with 33% in patients taking daunorubicin 60 mg/m².[6,10] The effectiveness of the HAA regimen compared with daunorubicin 90 mg/m² still needs to be studied. We did not detect any effect of regimen on survival by genotype because of the small number of patients with mutation data available. Although we used simple randomisation methods and did not stratify patients by region, we did not detect any regional effects, or interactions between regions and treatment groups. We also tried to prevent selection bias by doing the trial at many centres nationwide, with a large sample size, strict inclusion and exclusion criteria, a central telephone randomisation system, and valid sampling methods.

Comorbidity is a confounder and other health-related factors—eg, concomitant drugs and lifestyle—can also affect prognosis. We did not analyse these factors, which is a limitation of our study. However, we believe that these risk factors were evenly distributed between groups because the groups were randomly assigned, we used a large sample, and other baseline characteristics did not differ greatly between groups.

Data for event-free survival were obtained after post-induction treatment, therefore the post-induction treatment used could have affected the data. We believe that this effect is weak because we had a large sample size and different post-induction treatments were evenly distributed among the three groups.

In summary, our results suggest that the HAA regimen could be an alternative induction treatment for untreated acute myeloid leukaemia (panel), particularly for those with favourable and intermediate cytogenetics.

Contributors

JJ, J-XW, ZC, and S-JC designed the study, searched the published work, analysed and interpreted data, and wrote the report. F-FC and YT collected, analysed, and interpreted data, and wrote the report, with assistance from YS. Y-JL interpreted data and wrote the report. W-MN did the randomisation and assigned patients to treatment groups. D-PW, JH, J-FZ, J-DH, J-MW, J-YL, X-JH, JM, C-YJ, X-PX, K Yu, H-YR, Y-HZ, H-YT, H-FW, Y-CM, X Du, and B-AC enrolled patients, and collected and interpreted data. All authors reviewed the report and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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