Low-dose clofarabine in combination with a standard remission induction in patients aged 18-60 years with previously untreated intermediate and bad-risk acute myeloid leukemia or high-risk myelodysplastic syndrome: combined phase I/II results of the EORTC/GIMEMA AML-14A trial

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Supplemental material and methods

Study design

The combined phase I and II part of the trial, exploring the efficacy of clofarabine of 10 mg/m^2/day, was performed in 8 centers. After the maximum tolerated dose was reached in the phase I of the trial, additional patients were randomized in the phase II part of the trial using a 1-sample Fleming design. The statistical considerations were the following: P0 was 65%; P1 was 85%; beta error was 0.05 (actual one 0.07) and alpha error was 0.15 (actual one 0.12). Thus, for each of the arms A and B, the regimen was considered as active and feasible if ≥ 23/30 (76.7%) patients achieved a CR/CRi. A total of 30 patients were required in each arm (24 patients in addition to the 6 from the phase 1 of the trial using the same dosage of clofarabine).

The protocol was approved by the EORTC Protocol Review Committee and by the Ethical Committee of each participating center. Patients were prospectively randomized at the EORTC Headquarters after signed written informed consent was obtained according to ICH/GCP and national/local regulations. Randomization was stratified by institution and by presence of any of the following poor prognostic features known at the time of inclusion: white blood cells (WBC) at diagnosis >=100 x 10^9/L, very high-risk cytogenetics (defined as either monosomies 5, 7, or 5q-, 7q-, abn(3), t(6;9), t(9;22), or complex abnormalities (>3 abnormalities)), or FLT3-ITD positivity.

Comparison with a historical matched cohort of patients

The rate of CR/CRi after 1 or 2 cycles of induction chemotherapy as well as OS and Relapse-free survival (RFS) in the current study were compared with a cohort of comparable patients from the standard arm of the previous EORTC/GIMEMA study (AML-12)[1]. They met the same inclusion criteria as current AML-14A patients, and were from the centers that contributed patients to the current study. These analyses were not

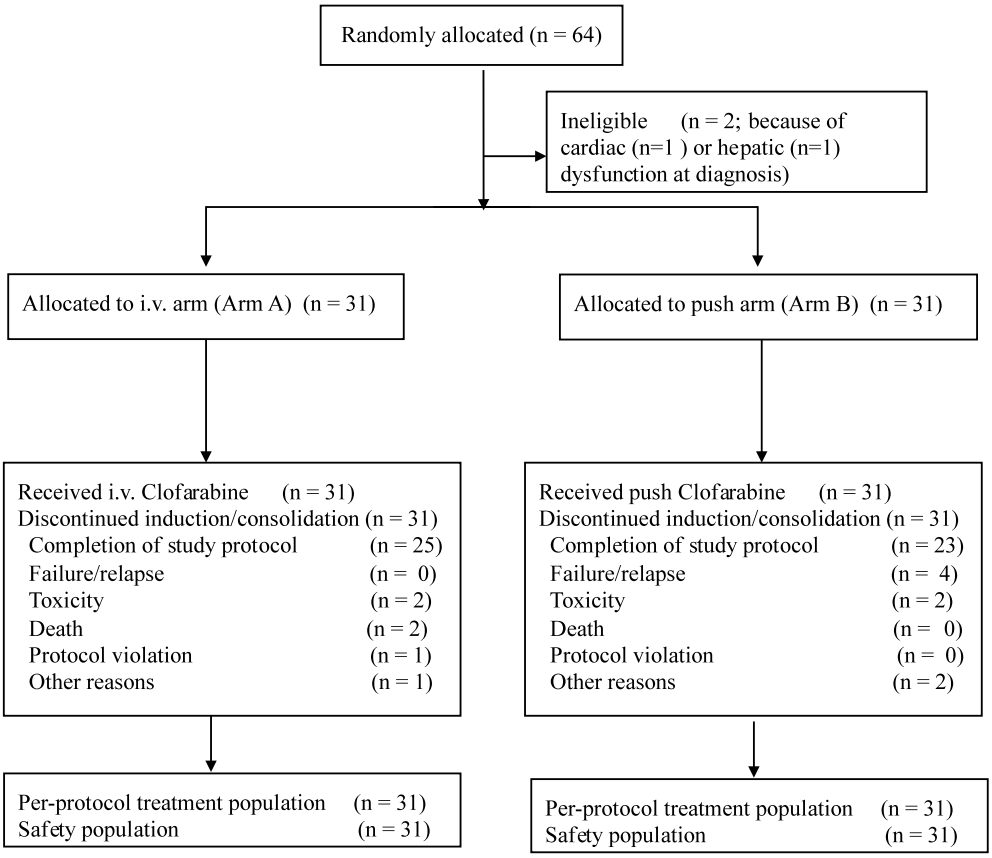
planned beforehand in the protocol. The standard arm of the AML-12 trial consisted of remission induction including Ara-C (100 mg/m^2 per day as continuous i.v. infusion for 10 days) plus daunorubicin (50 mg/m^2 per day as a 5-minute push injection on days 1, 3, and 5) plus etoposide (50 mg/m^2 per day by 1-hour i.v. infusion on days 1 through 5). Post-remission consolidation therapy consisted of intermediate-dose Ara-C (500 mg/m^2 every 12 hours as a 2-hour i.v. infusion on days 1 through 6) plus daunorubicin (50 mg/m^2 per day as a 5-minute push injection on days 4 through 6). Recommended post-consolidation treatment was as in the current protocol.

Stastistical analyses

Time to hematologic recovery from the start of the first induction course was assessed in patients who achieved a CR/CRi. The duration of OS was calculated from the date of randomization until death. RFS was calculated as the time from CR/CRi until the first relapse or death. The Kaplan-Meier method was used to estimate time-to-event outcomes. One-year OS and RFS rates and medians were presented with 95% confidence intervals (CI) based on the Brookmeyer and Crowley method[2]. Cumulative incidences of relapse or of death in CR/CRi were estimated from the date of CR/CRi achievement until either relapse or death without relapse by using competing risk methods[2]. Comparison of CR/CRi rate in current AML-14A patients and in comparable historical AML-12 patients was carried out with Fisher's exact test. SAS 9.3 software (SAS Institute Inc. Cary, NC) was used for the statistical analyses.

Supplemental Results

Supplemental figure 1. Disposition of patients in each arm of AML-14A study.



Supplemental Table 1. Baseline patients and historic controls (patients treated in the standard arm of the EORTC/GIMEMA AML-12 study) characteristics.

	Study	
	AML-14A (n=62)	**AML-12 (n=201)**
Gender, # of patients (%)		
Male	27 (43.5)	100 (49.8)
Female	35 (56.5)	101 (50.2)
Age, # of patients (%)		
15-45 years	26 (41.9)	91 (45.3)
46-60 years	36 (58.1)	110 (54.7)
WHO performance status, # of patients (%)		
0	46 (74.2)	125 (62.2)
1	14 (22.6)	67 (33.3)
2+	2 (3.2)	9 (4.5)
Type of disease, # of patients (%)		
De novo AML or MDS	57 (91.9)	194 (96.5)
Secondary AML or MDS	5 (8.1)	7 (3.5)
WBC at diagnosis, # of patients (%)		
< 100 $x10^9$/L	57 (91.9)	174 (86.5)
≥ 100 $x10^9$/L	5 (8.1)	27 (13.4)
Cytogenetics[a], # of patients (%)		
Good risk with ≥ 100$x10^9$ WBC/L at diagnosis	0 (0)	4 (2)
Normal (or –Y) without FLT3-ITD	22 (35.5)	83 (41.3)
High / very high risk or FLT3-ITD	36 (58)	90 (44.8)
Unknown/ failure / missing	4[c] (6.5)	24 (11.9)
Bone marrow blasts (%)		
Median	60.5	63.0
Range	12-99	2-96

[a]Cytogenetics: good risk includes inv(16) or t(8;21) ; very bad risk includes complex abnormalitis (>3 abnormalities), monosomies 5, 7 and 5q-, 7q-, 3q, t(6;9), t(9;22), 11q23, t(9;11) ; bad risk includes all other chromosomal abnormalities.

Supplemental table 2. Comparison results from the AML14A study with a matched group of patients treated in the standard arm of the EORTC/GIMEMA AML-12 study [1].

	Study		***P****
	AML-14A	**AML-12**	
# of patients	62	201	
Response to induction #1, # of patients (%)			
CR / CRi	51 (82.3)	134 (66.7)	0.025
CR / CRi / PR	53 (85.5)	153 (76.1)	
Resistant disease, hypoplasia, death	9 (14.5)	48 (23.9)	
Response to inductions #1 / #2, # of patients (%)			
CR / CRi	52 (83.9)	146 (72.6)	0.092
PR, resistant disease, hypoplasia, death	10 (16.1)	55 (27.4)	
Allogeneic transplantation in CR1, # of patients [%]**	26 [50.0]	43 [29.5]	
One-year outcomes, % (95% CI)			
Overall survival rate	74.1 (61.3 - 83.3)	58.0 (50.9 - 64.5)	
Relapse-free survival rate**	61.5 (47.0 - 73.2)	54.1 (45.7 - 61.8)	
Relapse incidence**	23.3 (11.7 – 34.8)	37.7 (29.8 – 45.5)	
Death in CR incidence**	17.3 (7.0 – 27.6)	9.6 (4.8 – 14.4)	

*: Using the Fisher's exact test

**: Computed in patients who reached CR after induction

References

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