# Clofarabine in Combination with a Standard Remission Induction Regimen in Patients 18-60 Years Old with Previously Untreated Intermediate and Bad Risk Acute Myelogenous Leukemia (AML) or High Risk Myelodysplasia (MDS): Combined Phase I/II Results of the EORTC/Gimema AML-14A Trial

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**Abstract**

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**Background:** The prognosis of younger patients with intermediate/bad risk AML or high-risk MDS remains unsatisfactory. Although with current remission induction chemotherapy, 60-85% of patients achieves complete remission (CR), only 30-50% of them remains alive for more than 5 years. Clofarabine, a second-generation purine analog, is highly active as a single agent in AML. Willemze et al (Ann Hematol, 2014) recently reported the results of phase I of the AML-14A study and identified clofarabine at 10 mg/m$^2$/day for 5 days as the maximum tolerated dose (given either in a 1-h infusion or as push injection) in combination with cytosine arabinoside (Ara-C) and idarubicin. We herein report the final results of the combined phase I and II parts of the AML-14A study that explored the antitumor activity of clofarabine containing induction combination regimens at the aforementioned phase I selected dosage schedules.

**Methods:** Patients aged 18-60 years with intermediate/bad-risk AML or high-risk MDS (≥10% bone marrow blasts), adequate renal and hepatic function, and WBC count <100x10$^9$/L at baseline (short cytoreductive use of hydroxyurea was permitted if WBC count at diagnosis exceeded 100x10$^9$/l) were centrally randomized for remission induction chemotherapy (for 1 or 2 cycles) between 1-hr infusion (Arm A) or push injection (Arm B) of clofarabine administered at 10 mg/m$^2$ on days 2, 4, 6, 8 and 10 in combination with Ara-



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C (100 mg/m$^2$/day on days 1–10) and idarubicin (10 mg/m$^2$/day, on days 1, 3, and 5). One cycle of consolidation including Ara-C (500 mg/m$^2$ every 12 hrs on days 1-6) and idarubicin (10 mg/m$^2$/day on days 4, 5 and 6) was administered in patients who achieved a CR/CRi in both arms. Primary endpoint was the CR/CRi rate after 1 or 2 cycles of induction. The aim was to determine whether in each treatment group the true CR/CRi rate is > 65% or not. Using a Fleming design, the regimen was considered active if ≥ 23 out of 30 patients per arm achieved CR/CRi. Secondary endpoints included safety, CR/CRi rate after consolidation, hematopoietic recovery, ability of CD34 harvesting after consolidation, disease-free survival (DFS) and survival from CR/CRi, and overall survival (OS). Randomization was stratified by institution and by presence of poor prognostic features (WBC at diagnosis >=100 x 10$^9$/L or very high-risk cytogenetics/FLT3-ITD).

**Results:** A total of 64 patients was randomized: 12 in the phase I part and 52 in the phase II part of the study. Two patients did not meet the inclusion criteria and were excluded. Among the remaining 62 patients, 5 had high-risk MDS. Median age was 50 yrs (range 20-60). Baseline characteristics were well balanced between the two arms. The CR/CRi rate after induction was 84% (26 of 31 patients) in each arm (95% CI: 66-95%) (Table 1). In Arm A vs Arm B, the most frequent grade >2 non-hematological and non-infectious adverse events over the induction-consolidation period were anorexia (29% vs 32%), and diarrhea (26% vs 32%). Finally, during treatment period there were 2 toxic deaths in Arm-A and 1 in Arm-B.

| | Arm-A (n=31) | Arm-B (n=31) |
|---|---|---|
| CR/CRi after 1-2 courses of induction, # pts (%) | 23 (74) / 3 (10) | 25 (81) / 1 (3) |
| CR/CRi after 1 course of induction, # pts (%) | 23 (74) / 3 (10) | 24 (77) / 1 (3) |
| OS median (95%CI), yrs | 2.5 (1-NR) | NR |
| OS at 1-yr (95%CI), % | 74 (55-86) | 74 (55-86) |
| # of infectious episodes with G3-4 neutropenia / # of patients with infection episodes | 47 / 30 | 59 / 31 |
| **In patients who achieved CR/CRi** | | |
| Time to recovery from start of course 1 | | |
| # of days with neutrophils<0.5x10$^9$/L, median (range) | 28 (22-96) | 27 (20-50) |
| # of days with neutrophils <1 x10$^9$/L, median (range) | 31 (22-99+) | 29 (21-50) |
| # of days with platelets < 20x10$^9$/L, median (range) | 28 (24-83) | 27 (23-44) |
| # of days with platelets < 100x10$^9$/L, median (range) | 31.5 (24-99+) | 31 (24-51) |
| # of patients given allogeneic / autologous stem cell transplantation | 11/0 | 14/2 |
| DFS, median (95%CI), yrs | 1.5 (0.6-NR) | NR |
| DFS at 1-yr (95%CI), % | 58 (37-74) | 65 (44-80) |
| relapse incidence at 1-yr (95%CI), % | 23 (7-39) | 19 (7-40) |
| death in CR incidence at 1-yr (95%CI), % | 19 (4-34) | 15 (2-29) |

**Table 1:**

Patient outcomes. Median follow-up was 1.8 (range, 1 – 5.25) yrs.

NR= not reached.

**Conclusions:** The 2 tested clofarabine (5x10 mg/m$^2$) containing regimens yielded an impressive (84%) CR/CRi rate among patients with intermediate/bad-risk AML and high-risk MDS patients. Toxicity profiles in the two arms appeared relatively comparable.

**Disclosures Off Label Use:** Clofarabine was used off label..

- * Asterisk with author names denotes non-ASH members.



Back to top



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