Efficacy of conventional-dose cytarabine, idarubicin and thioguanine (IAT) versus intermediate-dose cytarabine and idarubicin (IdAraC-Ida) in the induction treatment of AML: long-term results of the prospective randomized nationwide AML-2003 study by the Finnish Leukemia Group

Running title (40 characters): IAT versus IdAraC-Ida induction in AML

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Data availability statement

Anonymized dataset supporting findings in this study may be provided upon reasonable request from the corresponding author.

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1. What is the new aspect of your work?

To introduce long-term results of risk group and **measurable** residual disease **(MRD)** guided treatment algorithm by Finnish Leukemia Group.

2. What is the central finding of your work?

Randomization between the two induction arms (IAT and IdAraC) did not have a significant effect on prognosis whilst **MRD** and the risk classification-based treatment affected the outcome of the patients.

3. What is (or could be) the specific clinical relevance of your work?

Intensified treatment strategies including an allogeneic hematopoietic stem cell transplantation for patients with **MRD,** or high-risk features yielded favorable results compared with other publications.

Abstract

Objectives

AML-2003 study sought to compare the long-term efficacy and safety of IAT and IdAraC-Ida in **induction chemotherapy of** acute myeloid leukemia (AML) and introduce the results of **an integrated genetic and clinical risk classification** guided treatment strategy.

Methods

Patients were randomized to receive either IAT or IdAraC-Ida as the first induction treatment. Intensified post-remission strategies were employed based on measurable residual disease (MRD) and risk classification. Structured questionnaire forms were used to gather data prospectively**.**

Results

A total of 356 AML patients with a median age of 53 years participated in the study. Long term overall survival (OS) and relapse-free survival (RFS) were both 49 % at 10 years. The median follow-up was 114 months. No significant difference in remission rate, OS or RFS was observed between the two induction treatments. Risk classification according to the protocol, **MRD** after the first and the last consolidation treatment affected the **OS** and **RFS** significantly ($P < 0.001$).

Conclusions

Intensified cytarabine dose in the first induction treatment was not better than IAT in patients with AML. Intensification of post-remission treatment in patients with clinical risk factors or MRD seems reasonable, but randomized controlled studies are warranted in the future.

Keywords

AML, induction chemotherapy, measurable residual disease, allogeneic stem cell transplant, randomized, nationwide, survival, long-term follow-up

Introduction

Finnish Leukemia Group (FLG) has conducted prospective comparative studies in patients with acute leukemia for decades and used systematical questionnaire forms to collect data regarding achievement of remission, treatment-related toxicity and long-term survival. In medically fit patients with acute myeloid leukemia (AML), treatment with cytarabine and anthracycline has been the backbone of the induction protocol for decades with complete remission (CR) rates ranging between 60-80 % (1, 2). Relapses and treatment related toxicity are the major causes of acute mortality and morbidity in AML-patients. The AML-92 protocol by FLG evaluated the efficacy of idarubicin-based induction regimen in *de novo* AML-patients (3). The goals of the current AML-2003 study were to ascertain whether induction treatment with shorter but more intensive dosing of cytarabine in addition to idarubicin (IdAraC-Ida regimen) would lead to longer relapse-free survival, longer overall survival and possibly less toxicity when compared with idarubicin, conventional-dose cytarabine, and thioguanine treatment (IAT-regimen). The goal was also to assess how the dose of cytarabine affects the quality and length of remission in AML-patients.

Chromosomal and genetic aberrations in the leukemic clone have been shown to influence outcomes in AML-patients (1). Molecular and flow cytometric markers also enable monitoring of **measurable** residual disease (MRD) below the detection level of cytological methods. MRD guided treatment strategies include allogeneic hematopoietic stem cell transplantation for patients with persisting or rising MRD during consolidation therapy and treatment of post-transplant MRD with donor lymphocyte infusions, hypomethylating agents and tapering of immunosuppression. Clinical variables such as response to first induction cycle, high leukocyte count at diagnosis, the presence of extramedullary leukemia or

treatment-related leukemia also influence the risk of relapse and mortality in AML (4-7). The current study included also patients with secondary AML. For this study, a risk classification was created combining known genetic risk markers with clinical variables. Improved relapse-free survival (RFS) has been implicated (8) in patients with core-binding factor (CBF) AML treated with gemtuzumab ozogamicin (GO). In the AML-2003 study, GO was used in some CD33-positive transplant-ineligible patients with residual disease. In 2010 GO was withdrawn from the market due to toxicity, which ultimately resulted in very few patients receiving this medication during the treatment protocol.

The goal of this nationwide prospective study was to ensure that patients with AML which have adverse features receive the most intensive treatment and also to assess whether the risk classification-based treatment protocol would improve treatment results in AML-patients in comparison with the previous AML-92 protocol (3).

Materials and methods

Patients

A total of 359 consecutive patients with newly diagnosed AML between 16-65 years of age were recruited by FLG in the prospective AML-2003 study between November 2003 and November 2011. Patients were randomized to receive either IAT or IdAraC-Ida as the first induction treatment. This was a nationwide study including all five Finnish tertiary hospitals and two secondary hospitals (Vaasa Central Hospital and Satakunta Central Hospital). Only patients eligible for intensive chemotherapy were recruited (no signs of severe kidney, liver, heart or other organ failure unrelated to leukemia). Exclusion criteria also included: acute promyelocytic leukemia, blast crisis following chronic myeloid leukemia, pregnancy and breastfeeding, serious psychiatric illness and low compliance to treatment. Three patients were excluded from the analysis (two patients with blast crisis following chronic myeloid leukemia and one due to insufficient data) leaving a study population of 356 patients with median age of 53 years. Characteristics of patients enrolled are shown in Table 1a. Unlike the previous study by FLG (AML-92), patients with AML after myeloproliferative neoplasm, AML with multilineage dysplasia, and therapy-related AML were included in this study. All patients gave their written informed consent, and the study was approved by the ethical boards of all participating centers and by the Finnish Medicines Agency and was conducted according to the Helsinki Declaration.

Diagnosis

AML was diagnosed using standard cytological criteria according to French-American-British (FAB) classification (9) and by multiparameter flow cytometry (MFC) using standard lineage markers (appendix 1.). Karyotype analysis, fluorescence in-situ hybridization (FISH), polymerase chain reaction (PCR) and fusion gene analysis were undertaken to find the most suitable marker for monitoring MRD and for risk stratification. MFC with leukemia-associated aberrant immunophenotypes (LAIP) was also used for evaluating **MRD** in suitable patients. Quantitative PCR analysis of nucleophosmin 1-gene (NPM1) was gradually introduced to clinical practice from the year 2005. World Health Organization-classification (WHO) of AML was used after the results of cytogenetic studies (10).

The patients were categorized into three leukemia risk groups: low, intermediate and high risk according to cytogenetic abnormalities (11, 12) and clinical risk variables such as extramedullary disease, blood leukocyte count over 100 x 10^9/L and disease status after the first induction treatment (Table 1b). Median ages in different risk groups were: 43.7 years (low-risk), 52.8 years (intermediate-risk) and 54.5 years (high-risk). Risk classification affected the treatment of patients in the AML-2003 protocol: allogeneic hematopoietic stem cell transplantation (allo-HSCT) was offered to eligible patients in the intermediate- and high-risk groups. Patients not proceeding to allo-HSCT in these risk groups received a higher cytarabine dose during consolidation cycles II-III.

Data collection

Data were collected prospectively on all patients during each treatment cycle and during follow up. The following information was used for further statistical analysis: age at the time of diagnosis, gender, comorbidities, FAB and 2002 WHO classification of AML, laboratory

values at diagnosis, presence of extramedullary disease, genetic risk stratification according to European LeukemiaNet (ELN), randomization group in induction, neutropenic days (absolute neutrophil count, ANC < 0.5 x 10^9/L), hospital days, treatment status after each cycle, presence of residual disease in the bone marrow, allo-HSCT status, relapse and survival status. Statistical analysis for treatment toxicity also included the following: the WHO classification of performance status, severity of infection and gastrointestinal (GI), kidney, liver and central nervous system (CNS) toxicity. Whether death was attributed to leukemia, infection, treatment toxicity or other cause was determined by the treating physician.

Chemotherapy Protocol

Induction

Description of the chemotherapy protocol is given in greater detail in appendix 2. In short, after diagnosis of AML patients were randomized into two different induction treatments (IAT or IdAraC-Ida). Central randomization was done independently for each centre using sealed, numbered envelopes. Patients < 60 years of age and ≥ 60 years of age were randomized separately. If patient was considered a candidate for allo-HSCT, GO was withheld during induction and consolidation chemotherapy. The second induction treatment with mitoxantrone, etoposide and intermediate-dose cytarabine (MEA +/- GO) was given only to patients with bone marrow blasts > 10 % after the first induction. Patients with bone marrow (BM) blast count < 10 % moved on to consolidation treatments.

Consolidation

Chemotherapy protocol included three consolidation treatments for all risk groups (Figure 1.). First consolidation included high-dose cytarabine and idarubicin (HDAraC-Ida), the second mitoxantrone and cytarabine according to risk the group (Mito-IDAraC or Mito-HDAraC), and the third consolidation included m-amsacrine, conventional-dose cytarabine and etoposide (MACE). A fourth consolidation treatment with idarubicin, conventional-dose cytarabine and etoposide (ICE) was given only to patients in the high-risk group. GO was given in consolidation treatments II-IV if MRD was detected after the first consolidation treatment.

Antifungal prophylaxis, mostly fluconazole, was used during chemotherapy induced neutropenic phase (ANC < 0.5 x 10^9/L). Prophylaxis for bacterial infections was not used. Supportive care including the use of central venous catheter, blood products, granulocyte colony-stimulating factor (G-CSF) and the empirical treatment of infections was performed according to the policies of each participating hospital.

Allogeneic stem cell transplantation

Risk classification (according to the protocol) was used when evaluating the suitability of allo-HSCT as a treatment option. Allo-HSCT with HLA-matched sibling or unrelated donor was offered to eligible patients younger than 61 years of age with high-risk AML after the first consolidation treatment. Allo-HSCT with a suitable sibling donor was the preferred treatment after the first consolidation treatment for patients with intermediate-risk AML. If **MRD** was detected, Allo-HSCT with unrelated donor was also acceptable for intermediate-risk patients and with a sibling donor for low-risk patients (Figure 1.). For patients ≥ 61 years of age, eligibility for allo-HSCT was evaluated in transplant unit expert meetings on a patient-

to-patient basis. In eligible patients with a strong indication for allo-HSCT reduced intensity conditioning regimen (RIC) was considered.

Assessment of disease status and treatment-related toxicity

BM aspirate was taken after each treatment cycle for evaluation of morphological response. Per definition morphological CR was achieved when BM blast cell count was < 5 %, no blast cells with Auer rods or extramedullary disease was detected, ANC was > 1.0 x 10^9/L and platelets > 100 x 10^9/L (2). Relapse was defined as BM blast count ≥ 5 %, reemergence of blast cells in peripheral blood or detection extramedullary disease after initial remission. **MRD** status was first assessed after the first consolidation treatment and then after each cycle. **MRD** was considered significant for treatment strategies if the proportion of leukemic cells was over 0.3 %. The most suitable marker for monitoring **MRD** (FISH, MFC, PCR) was chosen on a patient-to-patient basis and this marker was used throughout the study. Treatment-related toxicity was evaluated during each cycle according to the WHO-criteria.

Statistical Analysis

Primary outcomes were: CR with induction therapy (1-2 cycles), overall survival (OS) and relapse-free survival (RFS). OS was calculated from the date of diagnosis to the date of death or the date of last follow-up. RFS was calculated from the date of attainment of CR to the date of relapse, death, or the date of last follow-up on patients still alive in first CR. Secondary outcome was treatment-related toxicity. SPSS version 25 (Armonk, NY: IBM Corp.) was used for statistical analysis. χ^2 test or Fisher's exact test was used for comparison between binomial variables. For paired groups McNemar's test was used. All P-values are two-tailed. RFS and OS were evaluated in different treatment groups using a Kaplan-Maier estimate and differences between groups were evaluated with log-rank test for statistical significance.

Variables showing association with P < 0.05 in univariate analysis were chosen for multivariate analysis (Cox regression).

Results

Induction chemotherapy and IAT vs. IdAraC-Ida

After randomization 178 patients were allocated to receive IAT (conventional-dose cytarabine) and 178 patients to receive IdAraC-Ida as the first induction treatment. Previous exposure to chemotherapeutics (P = 0.015) and extramedullary leukemia (P = 0.033) were more common in the IAT group. A CR was achieved in 74 % of patients in the IAT-group and 75 % in the IdAraC-Ida -group (P = 0.903). Fifty-four patients (15 %) were refractory to the first induction treatment (27 patients in each group). Of them, 26 (48%) achieved CR after the second induction treatment (MEA +/- GO). Altogether, 90 % of patients in the IAT randomization group and 85 % in the IdAraC group achieved CR with 2 induction cycles (P = 0.198).

The median follow-up time for the living patients was 114 months (range 17 to 170 months). **Five-year OS in the IAT-group was 55 % and 10-year OS was 51 %. For patients in the IdAraC-Ida -group the 5-year and 10-year OS were 49 % and 47 %, respectively (log rank P = 0.407**, Figure 2.). RFS in chemotherapy-treated patients at 5 and 10 years for IAT-group and IdAraC-Ida -group was 45 %, 44 % and 39 %, 38 %, respectively. RFS did not differ between the two induction treatments (Figure 2, log-rank P = 0.452). After the first consolidation 38 % of patients were MRD-negative (< 0.1 %) in the IAT-group and 40 % in

the IdAraC-Ida –group (P = 0.663). After the last chemotherapy cycle there were no differences in the number of MRD-negative patients (64 patients in each group, 36 %).

During the first induction therapy there were four deaths (2 %) in the IAT-group and four deaths in the IdAraC-Ida -group (2 %). Severe GI toxicity differed significantly in the first induction treatment between IAT- and IdAraC-Ida -treatments (31 % vs. 20 %, respectively, P = 0.031). Two patients in the IAT group had WHO 2-3 CNS toxicity (0 patients in the IdAraC-Ida -group). The results and toxicity of the induction treatments in different treatment groups are detailed in Table 2.

Equal proportion of patients in the IAT-group (56 %) and in the IdAraC-Ida –group (56 %) went on to allo-HSCT.

Results for the treatment group as a whole

RFS and OS

OS for the whole group (356 patients) was 52 % at 5 years and 49 % at 10 years and for non-transplanted patients (n = 157) 41 % and 38 %, respectively. RFS for the whole group (n = 312) at 5 and 10 years was 50.0 % and 49.0 %. When patients transplanted in the first CR (n=142) were excluded, 5-year and 10-year RFS were 37 % and 36 %. OS and RFS in different risk groups (according to protocol, see Table 1b.) are shown in Figure 2. This classification increased the size of the high-risk group when compared to genetic risk classification alone (25 % vs. 63 %, P < 0.001). A significant difference in OS was seen between different protocol risk groups (P < 0.001). No difference in OS was detected in

patients who started induction during days 6-10 or 0-5 after the diagnosis of AML (log rank P = 0.979).

Toxicity

Highest rate of severe GI toxicity (WHO 3 or over) was reported in the first induction treatment (25 %, 79/312 patients) and in the third consolidation treatment (24 %, 22/91 patients). Mortality during chemotherapy treatment was 8 % (28 patients) with **14 deaths during** induction treatments and **14 deaths during** consolidation treatments. Infection was the cause of death in 20 patients (5.6 %) and bacteria was detected in blood cultures in 80 % of patients with a fatal infection. Infection-related mortality was particularly high in patients receiving second induction treatment, (3 patients/5.6 %). Comorbidities seemed to be more frequent in patients with a fatal infection (65 % vs. 46 %, P = 0.109) and half of these were over 60 years of age (10 patients, P = 0.011).

Allo-HSCT

Altogether 199 patients underwent allo-HSCT (56 %). The mean age was 47 years. Percentages of patients proceeding to allo-HSCT according to the risk groups by the protocol were: 28 % in the low-risk group, 46 % in the intermediate-risk group and 62 % in the high-risk group. Stem cell donor was an HLA-matched sibling in 86 patients (43 %), matched unrelated donor in 111 patients (56 %) and cord blood in two patients (1 %). Timing of allo-HSCT was after induction treatments in 10 patients (5 %), after the first or second consolidation treatment in 124 patients (62 %), after the third consolidation treatment in 11 patients (6 %) and at a later time point in 31 patients (16 %). Sixteen patients (8 %) had a relapsed or refractory disease status prior to allo-HSCT. Twenty-five patients (13 %) died due

to complications of allo-HSCT. Altogether thirty patients (15 %) died in first CR after allo-HSCT.

When excluding patients with primary refractory leukemia, OS was significantly better in transplanted patients vs. non-transplanted patients (Figure 3a., log-rank $P < 0.001$) although transplanted patients tended to be younger. Five-year OS in transplanted patients 60 years of age or older was 52 %. In patients who underwent second induction treatment and **responded to treatment** (blasts under 10 % according to protocol, n = 32), long term survival was poor without allo-HSCT (5-year survival 9 % vs. 38 % in allo-HSCT recipients).

There was no significant difference in OS between patients receiving sibling transplants vs. MUD-transplants (5-year OS 57.0 % vs. 62.9 %, respectively, Figure 3c. log rank $P = 0.382$) but relapse-free survival was better in sibling transplant recipients ($P = 0.047$, Figure 3d.).

MRD

At diagnosis, MFC marker for monitoring **MRD** was detected in 166 patients (46.6 %) and quantitative PCR marker in 123 patients (34.6 %). A sensitive marker for monitoring **MRD** with either MFC or quantitative PCR was found in 233 patients (65.4 %). **MRD** monitoring with FISH was available on 184 patients (51.7 %). In patients under 60 years of age (n = 271) and over 60 years of age (n = 85), the prevalence of a quantitative PCR marker was not significantly different (35.8 % vs. 30.6 % respectively, $P = 0.379$). The same was true also for MFC as a marker for **MRD** (56.1 % vs. 45.1 %, $P = 0.103$). Prevalence of MFC marker in the low, intermediate and high-risk groups (according to protocol, Table 1b.) was 51.9 %, 53.9 % and 53.6 %, respectively.

OS in patients with MRD < 0.1 % (n = 134) after the first consolidation treatment was better than in patients (n = 67) with **MRD** ≥ 0.1 % (5-year OS 68.4 % vs. 44.8 %, respectively, Figure 4a. log-rank P < 0.001). In patients who did not undergo allo-HSCT and for whom marker for MRD was available (n = 86), the difference in overall survival was even more substantial (5-year OS 77.0 % vs. 31.0 %, Figure 4b. log-rank P < 0.001). OS was also better in patients with **MRD** < 0.1 % after the last chemotherapy cycle when compared to patients with **MRD** 0.1 % - 1 % (P = 0.027).

Multivariate analysis with following variables was undertaken: **extramedullary leukemia, previous exposure to chemotherapy**, karyotype risk group (taking in to account only chromosomal changes according to Table 1b.), complex karyotype, protocol risk group, age and **MRD** after last chemotherapy cycle. Variables that independently correlated with OS **were MRD status under 0.1 % (P < 0.001), no marker for MRD (HR 2.8, CI 95 % 1.8 – 4.2), MRD > 1.0 % (HR 5.1, 2.9 – 9.2) and age (P < 0.001, HR increase of 4.3 % per patient year).** Multivariate analysis of RFS after the last chemotherapy cycle with same variables revealed **MRD** under 0.1 % or over 1.0 %, no marker for MRD and age to be statistically significant. In patients with **MRD** under 0.1 % after the last chemotherapy cycle, OS was better in patients not proceeding to allo-HSCT (log rank P = 0.045).

Discussion

Earlier AML studies suggested that higher cytarabine doses in first induction treatment might prolong remission duration and disease-free survival (14, 15). In this study, no significant difference in OS, RFS, CR rate or induction deaths was seen between patients receiving IAT or IdAraC-Ida as the first induction treatment. Despite randomization, patients receiving IAT as induction treatment were significantly more often exposed to chemotherapy before the diagnosis of AML and extramedullary manifestations of the disease were also more prevalent. Treatment-related intestinal toxicity seemed to be more common in the IAT-group. In the IdAraC-Ida -group, exposure to chemotherapeutics was shorter than in the IAT-group, which might explain some of the difference in the GI toxicity. In some studies, the addition of a third chemotherapeutic agent to induction chemotherapy has been associated with more diarrhea in acute leukemia patients with varying results regarding survival and achievement of CR (16, 17). Infectious complications in this protocol have been discussed in a previous publication (18) and no significant differences were seen between different induction therapies. Current study also showed that OS did not differ in patients with time to induction 0-5 vs. 6-10 days suggesting that in most patients without acute hematological emergency (e.g., leukostasis) it is safe to establish control of acute infections and wait for results of cytogenetic and molecular studies before initiation of induction treatment. Similar results were also seen in a recent multicenter study (19).

This study introduced **an integrated genetic and clinical risk classification**, which divided patients into three risk groups: low, intermediate and high-risk groups. This risk

classification increased the proportion of patients in the high-risk group compared to genetic risk factors alone. Allo-HSCT with MUD or sibling transplant was the preferred treatment for patients in the high-risk group and altogether 199 patients (56 %) underwent allo-HSCT. One of the study goals was to compare the survival parameters with the previous FLG treatment protocol (AML-92). In the AML-92 study (3), patients transplanted in the first CR were excluded from the analysis. The 5- and 10-year OS for non-transplanted patients were 43 % and 37 % and 5-year and 10-year RFS were 40 % and 32 % in the AML-92 study. The rates of 5-year and 10-year OS (41 % and 38 %) and RFS (37 % and 36 %) in non-transplanted patients were similar in our study. **When transplanted patients were taken into account in a retrospective analysis, 5-year and 10-year OS were significantly better in the AML-2003 study compared to AML-92 (52 % vs. 45 % and 49 % vs. 37 %, log-rank P = 0.012).** Treatment results in the AML-2003 study can been seen encouraging as the patient cohort included high-risk AML patients with previous MDS (8 %) and therapy-related AML (7 %) which were excluded from the previous study. Long term OS and RFS observed in our study (49 % and 49 % at 10 years, respectively) compares favorably with other studies (16, 20).

Markers of **MRD** varied between patients. In patients with multiple suitable **MRD**-markers, most often only one method of measurement was selected for evaluation of **MRD**. Therefore, this study used a composite marker of **MRD** (quantitative PCR, MFC, FISH). Quantitative PCR-based methods became gradually available during study period which might explain why PCR-marker was used only in approximately 1/3 patients. This study shows that survival in patients with **MRD** under 0.1 % after the first consolidation therapy and at the end of chemotherapy is better than in patients with **MRD** ≥ 0.1 % at these time points. There were three patients with 0.3 – 1 % **MRD** after the second consolidation treatment, all of whom

were transplanted and alive during the last point of follow up. When transplanted patients were excluded, the survival seemed to consistently decrease with increasing amount of **MRD** within interval under 0.1 % - 1 % (at any time during treatment).

The chemotherapy protocol encouraged allo-HSCT in patients whose risk of relapse was high due to genetic factors and/or clinical risk factors and a significant portion of patients underwent allo-HSCT (56 %). This is a relatively high number compared to other AML studies of this era (21-24). OS of patients in allo-HSCT group was 59.1 % at the end of follow-up. Allo-HSCT correlated with better OS in patients who **achieved blast count < 10 %** only after second induction treatment. Interestingly, sibling transplants were associated with favorable RFS, but OS benefit was not observed.

Study design had some limitations regarding the comparability of interventions. For example, treatments were guided by the presence of **MRD**, but no control group was appointed for those with intensified treatment during consolidation therapy or for those proceeding to allo-HSCT due to **MRD**. Comparison with historical controls is also of limited value due to differences in AML characteristics. In this study patients with high-risk features were allocated to receive GO, which is not advised in the light of current treatment guidelines (1, 25). Strengths of this study include the prospective nation-wide multicenter setting, equal quality of care in different hospitals and the long follow-up, which allows the assessment of certain complications on survival that are not commonly included in comparative treatment studies of AML.

In conclusion, no significant difference was seen in efficacy between IAT and IdAraC-Ida induction treatments and the long-term results are comparable and good in both treatment groups. The results of this study do not encourage the use of higher cytarabine dose during

first induction treatment which is in accordance with ELN 2017 guidelines. **MRD** has a significant effect on survival especially in non-transplanted patients and it seems reasonable to guide treatment strategies based on **MRD**.

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Conflict of interest:

The principal author owns shares in AbbVie company. Other authors have no conflicts of interest to declare.

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Table 1a. Characteristics of patients enrolled in the AML-2003 treatment study

	All	%	IAT	IdAraC-Ida	P-value
Patient: n, %	356	100			0.168
Female	183	51	98	85	
Age[a]: median, range	53	16-65			0.794
< 45 years	113	32	59	54	
45-59.9 years	158	44	76	82	
60-65.9 years	85	24	43	42	
Comorbidity	167	47	88	79	0.914
Cardiovascular disease[b]	64	18	32	32	1.000
Chronic lung disease	16	5	8	8	1.000
Diabetes	13	4	5	8	0.719
Previous nonmyeloid malignancy	21	6	14	7	0.115
Previous exposure					
Radiation	9	3	6	3	0.311
Chemotherapy	31	9	22	9	**0.015**
Solvent or pesticide	15	4	5	10	0.187
WHO performance status					0.719
GR0	72	20	35	37	
GR1	184	52	89	95	
GR2	67	18	39	28	
GR3	11	3	5	6	
GR4	5	1	3	2	
Unknown	17	5	7	10	
AML classification					0.219
AML with a balanced translocation	58	16	30	28	
AML with multilineage dysplasia	32	9	12	20	
AML following MDS	29	8	15	14	
Treatment-related AML	25	7	17	8	
AML, not otherwise characterized	209	59	104	105	
M0	20	6	8	12	
M1	49	14	25	24	
M2	58	16	29	29	
M4	20	6	13	7	
M5	49	14	26	23	
M6	2	1	0	2	
Unknown	11	3	3	8	
Acute leukemia, unknown cell line	1	0.02	0	1	
Unknown	2	1	0	2	
Risk group[c]					0.742
Favourable	65	18	33	32	
Intermediate	192	54	100	92	
Adverse	90	25	42	48	
Unknown	8	2	3	5	
NPM and FLT3 status					0.462
NPM+	34	10	19	15	
FLT3+	15	4	6	9	
FLT3+ and NPM+	17	5	7	10	

Clinical risk factors					
Blood leucocytes > 100 x 10^9/l	37	10	18	19	0.862
Extramedullary leukemia	59	18	37	22	**0.033**

[a] At the time of the first induction
[b] Including treated hypertension
[c] According to 2010 European LeukemiaNET recommendations (2)

Table 1b. Combined cytogenic, molecular genetic and clinical risk classification according to the AML-2003 treatment study (Finnish Leukemia Group)

Low risk

Patient with *de novo* or secondary leukemia **and all of the following:**

- t(8;21), inv(16)(p13;q22) **or** t(16;16)(p13;q22) +/- one other genetic abnormality that is not a high risk abnormality **and**
- Absolute leukocyte count < 100 x 10^9 at diagnosis and no signs of extramedullary leukemia **and**
- Bone marrow blast count ≤ 10 % after the first induction treatment.

Intermediate risk

Patients with de novo leukemia **and all of the following:**

- Normal karyotype **or** +8, -Y, +6, del(12p) **or** other that is not a high-risk genetic abnormality **or** 2 genetic abnormalities excluding low- and high-risk abnormalities.
- **and** absolute leukocyte count < 100 x10^9 at diagnosis and no signs of extramedullary leukemia.
- **and** bone marrow blast count ≤ 10 % after the first induction treatment.

High risk

Patients with de novo or secondary leukemia and **one of the following:**

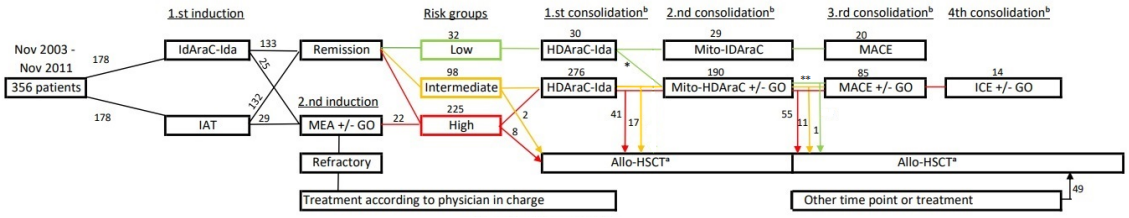
- -5, del(5q), -7, del7(q), inv(3q), t(3q21-26), abnormal 11q23, 20q, 21q, 17p, del(9q), t(6;9), t(9;22).
- ≥ 3 genetic abnormalities.
- t(8;21), inv(16) or t(16;16) and one of the aforementioned high risk abnormality.
- Secondary leukemia with intermediate risk karyotype, normal karyotype or unknown karyotype.
- Absolute leukocyte count > 100 x 10^9/l at diagnosis.
- Extramedullary leukemia.
- Minimally differentiated AML (FAB M0), acute erythroid leukemia (FAB M6), acute megakaryoblastic leukemia (FAB M7) or acute hybrid leukemia according to modified EGIL-classification (13).
- Multilineage dysplasia according to WHO classification
- AML after myelodysplastic syndrome or myeloproliferative disease (diagnosis at least 3 months before the diagnosis of AML)
- Bone marrow blast count > 10 % after the first induction treatment.

Table 2. Results of the first induction treatment and risk groups according to the AML-2003 study (Finnish Leukemia Group).

	Randomization group					Age group					
	IAT		IdAraC-Ida			< 45 years		45-59		60+	
Group	n	%	n	%	P-value	n	%	n	%	n	%
First induction treatment											
Complete remission	132	74.2	133	74.7	0.903	99	87.6	108	68.7	57	67.1
Blasts 5-10 %	12	6.7	10	5.6	0.659	4	3.5	13	8.2	5	5.9
Dysplasia-hypoplasia	3	1.7	4	2.2	0.702	2	1.7	3	1.9	2	2.4
Refractory	27	15.1	27	15.1	1.000	7	6.2	29	18.4	18	21.2
Death	4	2.2	4	2.2	1.000	1	0.9	4	2.5	3	3.5
Risk group					0.920						
Low risk	15,	8.4	17,	9.6		17,	15.0	10,	6.4	5,	5.9
Intermediate risk	50,	28.1	48,	27.0		35,	31.0	46,	29.3	17,	20.0
High risk	113,	63.5	113,	63.5		61,	54.0	101,	64.3	63,	74.1
Toxicity (WHO 3-4)											
Bowel	48	31.4	31	19.5	0.016	28,	24.8	40,	25.5	13,	15.3
Stomatitis	23	15.1	15	9.8	0.170	13,	11.5	15	9.6	9,	10.6
Kidney	1	0.6	1	0.6	1.000	0,	0.0	2,	1.3	0,	0.0
Liver	9	5.7	15	9.3	0.220	7,	6.2	15,	9.6	4,	4.7
Performance	87	56.5	86	56.9	0.940	51,	45.1	84,	53.5	47,	55.3
Infection	82	50.6	77	48.7	0.740	55,	48.7	73	46.5	31,	36.5
Death	3	1.7	3	1.7	1.000	1,	0.9	3	1.9	2,	2.4
Neutropenia days: median, range	23,	2-65	25,	9-53		25,	2-48	23,	9-65	24,	14-46
Thrombocytopenia days: median, range	22,	8-66	23,	2-55		23,	9-50	22,	2-66	21,	10-52
Highest CRP, range	182,	20-513	189,	9-448		177,	22-513	192,	9-492	182,	24-426
Hospital days: median, range	30,	18-67	32,	16-84		31,	19-82	31,	16-73	31,	21-84

Figures

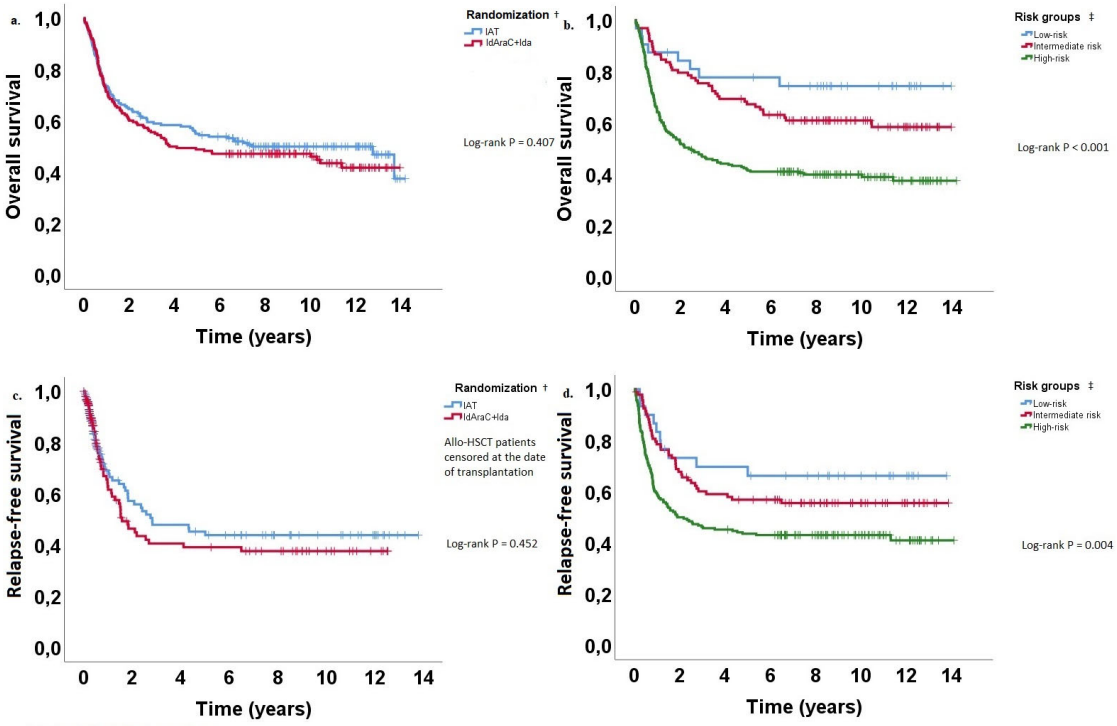
Figure 1. Flow chart of the 356 patients recruited in the AML-2003 study (Finnish Leukemia Group)



	< 60 years	≥ 60 years
IdAraC	1000 mg/m² (D1-4)	750 mg/m² (D1-4)
HDAraC	1500 mg/m² (D1-4)	750 mg/m² (D1-4)
Conventional-dose AraC	100 mg/m² (D1-9)	100 mg/m² (D1-7)
Idarubicin	12 mg/m² (D1, 3, 5)	12 mg/m² (D1, 3, 5)
Thioguanine	75 mg/m² (D1-9)	75 mg/m² (D1-7)

[a] Allogeneic hematopoietic stem cell transplantation
[b] Intrathecal cytarabine during consolidation for CNS leukemia risk groups (see appendix 2.).
* If residual disease > 0.3 %
** If residual disease > 0.3 %, allo-HSCT with sibling donor for low-risk patients and with matched unrelated donor for intermediate-risk patients

Figure 2. Overall survival and relapse-free survival in different treatment groups in the AML-2003 study (Finnish Leukemia Group)



† During the first induction treatment
‡ According to the protocol (See Table 1b.)

Figure 3. Overall survival and relapse-free survival in allogeneic stem cell transplanted patients in the AML-2003 study (Finnish Leukemia Group)

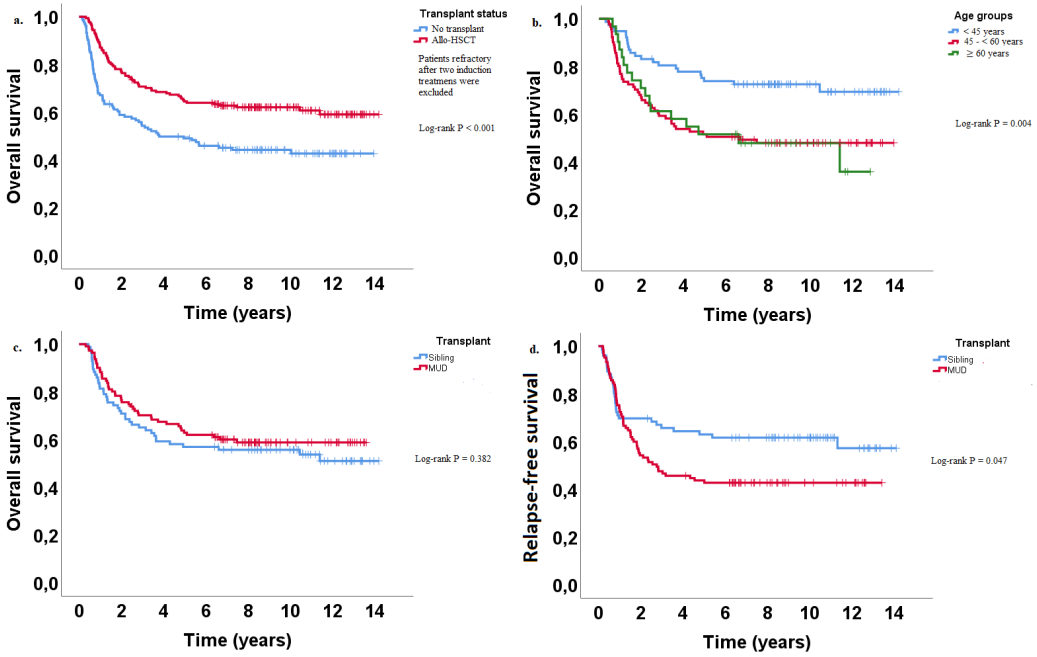


Figure 4. Measurable residual disease and overall survival in the AML-2003 study (Finnish Leukemia Group)