Prognostic impact of day 15 blast clearance in risk-adapted remission induction chemotherapy for younger patients with acute myeloid leukemia: long-term results of the multicenter prospective LAM-2001 trial by the GOELAMS study group

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ABSTRACT

Early response to chemotherapy has a major prognostic impact in acute myeloid leukemia patients treated with a double induction strategy. Less is known about patients treated with standard-dose cytarabine and anthracycline. We designed a risk-adapted remission induction regimen in which a second course of intermediate-dose cytarabine was delivered after standard "7+3" only if patients had 5% or more bone marrow blasts 15 days after chemotherapy initiation (d15-blasts). Of 823 included patients, 795 (96.6%) were evaluable. Five hundred and forty-five patients (68.6%) had less than 5% d15-blasts. Predictive factors for high d15-blasts were white blood cell count (P<0.0001) and cytogenetic risk (P<0.0001). Patients with fewer than 5% d15-blasts had a higher complete response rate (91.7% *vs.* 69.2%; P<0.0001) and a lower induction death rate (1.8% *vs.* 6.8%; P=0.001). Five-year event-free (48.4% *vs.* 25%; P<0.0001), relapse-free (52.7% *vs.* 36.9%; P=0.0016) and overall survival (55.3% *vs.* 36.5%; P<0.0001) were significantly higher in patients with d15-blasts lower than 5%. Multivariate analyses identified d15-blasts and cytogenetic risk as independent prognostic factors for the three end points. Failure to achieve early blast clearance remains a poor prognostic factor even after early salvage. By contrast, early responding patients have a favorable outcome without any additional induction course. (*ClinicalTrials.gov identifier NCT01015196*)

Introduction

In younger patients with acute myeloid leukemia (AML), standard induction chemotherapy consists of cytarabine by continuous infusion for seven days combined with daunorubicin or idarubicin for three days according to the so-called "7+3" regimen.[1,2] Many attempts have challenged this standard of care by adding a third drug, increasing the dose of cytarabine or increasing dose-intensity.[3,4] However, these strategies did not convincingly improve outcome and the sole significant modification of the original "7+3" has been recently established by increasing the dose of daunorubicin from 45 to 90 mg/m^2, which resulted in better outcome.[5,6] In this context, prognostic factors are mainly based on pre-treatment parameters that are both patient-specific and disease-related.[7] Among them, the cytogenetic classification remains the strongest criterion for predicting complete response (CR) achievement, relapse-free and overall survival, although mutations in the *FLT3, NPM1* and *CEBPA* genes have recently improved the prognostic classification of patients with a normal karyotype.[8] Thus, post-remission therapy stratification is currently based on chromosomal and molecular aberrations.[3]

Early response to therapy is a strong prognostic factor in acute lymphoblastic leukemia where the persistence of blasts in blood or bone marrow (BM) after the first seven or 14 days of treatment is highly predictive of disease recurrence.[9,10] In AML, early response to induction chemotherapy evaluated by residual BM leukemic cells during aplasia has also been shown to have a significant prognostic impact.[11,12] This has been particularly assessed in the setting of the double induction strategy developed by the German AML cooperative group (AMLCG) which demonstrated that early blast clearance 16 days after the beginning of chemotherapy was a major prognostic factor for remission and long-term outcome independent of pre-therapeutic parameters.[13] Conversely, it is not clear whether patients without residual BM blasts at Day 16 benefit from the second course systematically delivered in double induction schedules. In the setting of the standard

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"7+3", the prognostic impact of early blast clearance has been much less studied, although it is generally accepted that patients only achieving CR after two courses have a worse prognosis.[14,15] For patients showing persistent BM leukemia one week after the first induction course, the usual practice is to give a second course of a similar regimen ("7+3" or "5+2"). However, this strategy has not been well evaluated. It is not known whether "5+2" is equivalent to "7+3" or if a higher cytarabine dose could be of benefit. Furthermore, both the percentage of blasts and the timing of early evaluation are not clearly defined, and may vary according to different study groups.

In the LAM-2001 trial, we designed a risk-adapted induction chemotherapy based on bone marrow (BM) evaluation at Day 15.[16,17] If patients had 5% residual blasts or more, they systematically received a second induction course with intermediate-dose cytarabine, whereas patients with fewer than 5% blasts did not receive additional induction chemotherapy. Here, we assessed the prognostic impact of Day 15 blast clearance on the outcome of 795 younger AML patients enrolled in this trial.

Methods

Study population and treatment

This analysis is based on patients enrolled in the phase III prospective randomized LAM-2001 trial registered at *http://clinicaltrials.gov/ct* as no. *NCT01015196*.[16,17] In accordance with the Declaration of Helsinki, the study was approved by the Comité de Protection des Personnes ethics committee (i.e. IRB, Nantes, France; ID 2000/5/00). All patients provided written informed consent. Patients' eligibility, cytogenetic classification and study design have been reported elsewhere.[16] Cytogenetic analyses were performed according to the International System for Human Cytogenetic Nomenclature.[18] BM biopsies are not performed in French centers, neither for diagnosis (except in case of "dry tap") nor for response assessment. Patients received cytarabine 200 mg/m²/d for seven days in continuous 24-h infusion and either idarubicin 8 mg/m²/d for five days or daunorubicin 60 mg/m²/d for three days depending on first randomization. BM aspiration was performed on Day 15 (d15). No patient received G-CSF before d15. BM smears were assessed using May-Grünwald-Giemsa stains (and not flow cytometry) by cytologists of the GOELAMS study group on at least 200 cells.[19] Aplastic BM was considered as blast-free. Data obtained locally were used for immediate stratification (*i.e.*, second induction course at d17). Centralized collegial slide review did not modify significantly the original counts. Indeed, of 611 slide reviews, only 10 changes (1.6%) would have modified the patient's stratification. Thus, all locally-evaluated patients were used for the analysis. If less than 5% marrow blasts were present, evaluation for complete response (CR) was performed between Days 28 and 35. If there were 5% or more marrow blasts, a second induction course was given at Day 17. All patients in CR with an HLA-identical sibling were allocated to allogeneic stem cell transplantation (alloSCT) except those with core binding factor leukemia; others were scheduled to receive one or two autologous SCT (autoSCT).[16,17] The validation cohort included 152 AML patients treated at the University Hospital of Toulouse outside the LAM-2001 trial between 2000 and 2010. All patients received the same induction regimen with daunorubicin (60 mg/m², 3d; n=147) or idarubicin (8 mg/m², 5d; n=5) combined with cytarabine (200 mg/m², 7d), had a BM aspiration at d15 and received the second induction if d15 blasts were 5% or more including daunorubicin 35 mg/m² or idarubicin 8 mg/m² on Days 17 and 18 and cytarabine 1000 mg/m² bid on Days 17-20, followed by G-CSF until recovery of neutrophil.

Statistical analysis

Patients' characteristics were described using numbers and frequencies for qualitative data and median and range for quantitative data, and compared using χ^2 or Mann Whitney tests. Definitions of CR, induction failure, overall survival (OS), event-free survival (EFS), cumulative incidence of relapse (CIR) and relapse-free survival (RFS) are detailed in the *Online Supplementary Appendix*. Survival data were estimated by the Kaplan-Meier method and compared by the log rank test; differences in response rate and induction failures were compared between groups using the χ^2-test. Age, performance status, cytogenetics and d15 blasts were included in multivariate analyses. Multivariate analysis of response rate was conducted using logistical regression and a Cox model for EFS, RFS and OS. All reported *P* values were two-sided and $P<0.05$ was considered significant. Statistical analysis was performed on MedCalc software (Mariakerke, Belgium) or with the R-Forge for CIR.

Results

Patients

From November 2001 to April 2005, 832 untreated AML patients (≤ 60 years) were enrolled in 28 French centers. Ninety-seven percent had *de novo* AML. Nine patients were excluded.[16] Of the 823 patients who received induction treatment, 795 (96.6%) were evaluable for the analysis (Table 1). Median follow up among patients who were still alive at the date of last contact was 87.2 months (range 22.3-122.6). Five hundred and forty-five patients (68.6%) had less than 5% marrow blasts at d15 (d15 blasts). The median d15 blasts percentage in the 250 patients with 5% or more was 22% (range 5-100%). As compared to patients with d15 blasts fewer than 5% patients with 5% or more had a lower white blood cell count (WBC) ($5x10^9$/L, range 0.61-240 *vs.* $12.5x10^9$/L, range 0.04-351; $P<0.0001$) and a higher cytogenetic risk ($P<0.0001$) since 88 of 250 (35.2%) patients with 5% or more d15 blasts had an unfavorable karyotype *versus* 77 of 545 (14.1%) for patients with fewer than 5%. In multivariate analysis, among age, performance status, WBC and cytogenetic risk, independent predictive factors for d15 blasts 5% or more were low WBC (Odds Ratio (OR) 0.99, 95% Confidence Interval (CI): 0.98-0.99; $P<0.0001$) and poor cytogenetic risk (OR 2.55, 95%CI: 1.93-3.37; $P<0.0001$). The second course was delivered at d17 in 211 of 250 (84.4%) patients (Figure 1). None of the 545 patients with fewer than 5% d15 blasts received the second course.

Toxicity

The median time to neutrophil and platelet count recovery was significantly shorter in patients with fewer than 5% d15 blasts resulting in a shorter median duration of hospitalization (39 *vs.* 28 days; $P=0.0001$) (Table 2). Septicemias were also more frequent in patients with 5% or more d15 blasts. Death in aplasia occurred more frequently in patients with 5% or more d15 blasts than in patients with fewer than 5% (6.8% *vs.* 1.8%; $P=0.001$).

Outcome

The overall CR rate was 84.9%, significantly higher in patients with fewer than 5% d15 blasts (91.7%) than in

those with 5% or more (69.2%) (*P*<0.0001) (Table 1). Failure to reach CR (i.e. resistant disease) was higher in patients with 5% or more d15 blasts (24% *vs.* 6.1%; *P*<0.0001). In univariate analysis, age, cytogenetic risk and d15 blasts were significantly correlated with CR achievement whereas WBC and performance status had no impact. In multivariate analysis, age, cytogenetic risk and d15 blasts retained significance (Table 3). EFS was significantly longer for patients with fewer than 5% d15 blasts resulting in 5-year estimates of 48.4% (±2%) for the group with fewer than 5% and 25% d15 blasts (±3%) for the group with 5% blasts or over (Hazard ratio (HR) 1.87; 95%CI: 1.52-2.30; *P*<0.0001) (Figure 2A). For the 673 CR patients, 5-year RFS was 52.5% (±2.2%) in the group with fewer than 5% d15 blasts and 36.9% (±3.7%) in the group with 5% blasts or over (HR 1.43; 95%CI: 1.12-1.82; *P*=0.0016) (Figure 2B). The difference between both groups was also significant in 5-year CIR while there was no difference in the rate of death without relapse (*Online Supplementary Figure S1A*). There was a significant difference in OS with a 5-year estimate of 55.3% (±2.1%) in the group with fewer than 5% d15 blasts and 36.5% (±3.7%) in the group with 5% blasts or more (HR 1.69; 95%CI: 1.36-2.1; *P*<0.0001) (Figure 2C). EFS, RFS and OS according to the distribution of the percentages of d15 blasts are shown in Table 4. D15 blasts were entered into a multivariate model with other prognostic factors (age, cytogenetics, WBC and performance status). D15 blasts and cytogenetics remained independent prognostic factors for EFS, RFS and OS, age for EFS and OS, WBC for EFS and RFS (Table 3). After excluding the 39 patients with 5% blasts or more who did not receive the second course of chemotherapy, the same significant impact of d15 blasts on EFS, RFS and OS was observed (*data not shown*).

Impact of d15 blasts in patients with intermediate cytogenetic risk

The characteristics of the 458 patients with intermediate karyotype are presented in Table 5. The 326 patients (71.2%) with fewer than 5% d15 blasts had a lower median WBC, a lower resistant disease rate (5.5% *vs.* 22%) and a higher CR rate (92.3% *vs.* 70.5%) than patients with 5% blasts or more. Five-year EFS and 5-year OS were significantly longer for patients with fewer than 5% d15 blasts (Figure 3). The median RFS was 93.3 months for patients with fewer than 5% d15 blasts and 26.3 months for those with 5% or more, with 5-year RFS of 51.2% (±2.8%) and 38.5% (±5%), respectively (HR 1.33; 95%CI: 0.96-1.84; *P*=0.06). Five-year CIR was significantly lower in patients with fewer than 5% d15 blasts while there was no difference in the rate of death without relapse (*P*=0.045) (*Online Supplementary Figure S1B*). D15 blasts did not have a prognostic impact in terms of EFS, RFS and OS in patients with unfavorable cytogenetics (*data not shown*).

Impact of post-remission therapy

Of the 502 CR patients with fewer than 5% d15 blasts, 120 received an alloSCT and 184 an autoSCT. In allografted patients, 5-year RFS was 69.7% (±4%) as compared to 55.8% (±3.7%) in autografted patients (HR 0.65: 95%CI: 0.45-0.94; *P*=0.03) while there was no significant difference in 5-year OS (*Online Supplementary Figure S2A and B*). Of the 173 CR patients with 5% or more d15 blasts, 43 received an alloSCT and 58 an autoSCT. Five-year RFS (53±7.7% *vs.* 32.6±6%; HR 0.57; 95%CI: 0.34-0.94; *P*=0.035) and 5-year OS (57.6±7.6% *vs.* 41±6.5%; HR 0.55; 95%CI: 0.32-0.94; *P*=0.04) were significantly better in allografted patients (*Online Supplementary Figure S2C and D*).

Validation cohort

An independent cohort of 152 AML patients was used to validate the prognostic impact of d15 blasts with the 5% cut off (*Online Supplementary Table S1*). At d15, 65.1% of patients had fewer than 5% marrow blasts and their CR rate was 89.9% as compared to 73.6% in patients with 5% or more (*P*=0.01). Five-year EFS (45±5% *vs.* 24±7%; HR 1.65; 95%CI: 1.04-2.6; *P*=0.015), RFS (47.5±6% *vs.* 25±8%; HR 1.7; 95%CI: 1-2.96; *P*=0.02) and OS (49.6±5% *vs.* 25±8%; HR 1.6; 95%CI: 1-2.6; *P*=0.03) were significantly higher in patients with d15 blasts fewer than 5% (*Online Supplementary Figure S3*). A multivariate analysis was performed in the validation population and confirmed 5% or more d15 blasts as an independent prognostic factor for CR, EFS, RFS and OS (*Online Supplementary Table S2*).

Discussion

In the context of double induction strategy, early blast clearance has been fully assessed by the German AML cooperative group (AMLCG) that demonstrated that the

Table 1. Patients' characteristics.

	All patients n=795	Day 15 marrow blasts <5% n=545	Day 15 marrow blasts ≥5% n=250	*P*
Median age (range) years	47 (17-61)	46 (17-61)	48.5 (17-61)	NS
Male gender n (%)	409 (51.4)	278 (51)	131 (52.4)	NS
Performance status* n. (%)				
0-1	705 (88.7)	484 (88.8)	221 (88.4)	NS
2-4	86 (10.8)	59 (10.8)	27 (10.8)	
Median WBC (range) - x10⁹/L	9.3 (0.04-351)	12.5 (0.04-351)	5.0 (0.61-240)	<0.0001
Cytogenetics n. (%)				
Favorable	119 (15)	101 (18.5)	18 (7.2)	<0.0001
Intermediate	458 (57.6)	326 (59.8)	132 (52.8)	
Unfavorable	165 (20.8)	77 (14.1)	88 (35.2)	
Undetermined	53 (6.7)	41 (7.5)	12 (4.8)	
Day 15 marrow blasts				
Median % (range)	0 (0-100)	0 (0-4)	22 (5-100)	
0-4-n (%)	545 (68.6)	545 (100)	0	
5-10-n (%)	57 (7.2)	0	57 (22.8)	
11-20-n (%)	67 (8.4)	0	67 (26.8)	-
21-50-n (%)	65 (8.2)	0	65 (26)	
>50-n (%)	57 (7.2)	0	57 (22.8)	
NA	4 (0.5)	0	4 (1.6)	
2nd induction at d15 n. (%)	211 (26.5)	0	211 (84)	-
Complete response n. (%)	675 (84.9)	502 (92.1)	173 (69.2)	< 0.0001
Induction failure n. (%)	120 (15.1)	43 (7.9)	77 (30.8)	
Deaths in aplasia	27 (3.4)	10 (1.8)	17 (6.8)	0.001
Resistant disease	93 (11.7)	33 (6.1)	60 (24)	< 0.0001
AlloSCT n (%)	163 (20.5)	120 (22)	43 (17.2)	NS

*NA: files mentioned a significant residual leukemic infiltration at d15 but the percentage of blasts was not available; WBC: white blood cell count; alloSCT: allogeneic stem cell transplantation; NS: not significant. * Missing data, n=4. Resistant disease and deaths in aplasia were defined according to the Cheson criteria.[20]*

persistence of residual marrow blasts one week after completion of the first course was an independent prognostic factor.[11,13,21] Our study is the largest to date to assess the impact of early blast clearance in the context of the "7+3" schedule with a conditionally-delivered second induction course. We show here that early responders had improved 5-year EFS, RFS and OS by 23%, 15% and 19% as compared to non-responders. Thus, early response to therapy, which reflects both the pharmacodynamics and pharmacogenetics of the host and the biology of leukemic cells, has a major prognostic strength in AML, probably as important as cytogenetics or molecular alterations. Early blast clearance retained a highly significant impact in the intermediate-cytogenetic risk group in which mutations with prognostic value have been recently described. Because the detection of *FLT3* mutations was not manda-

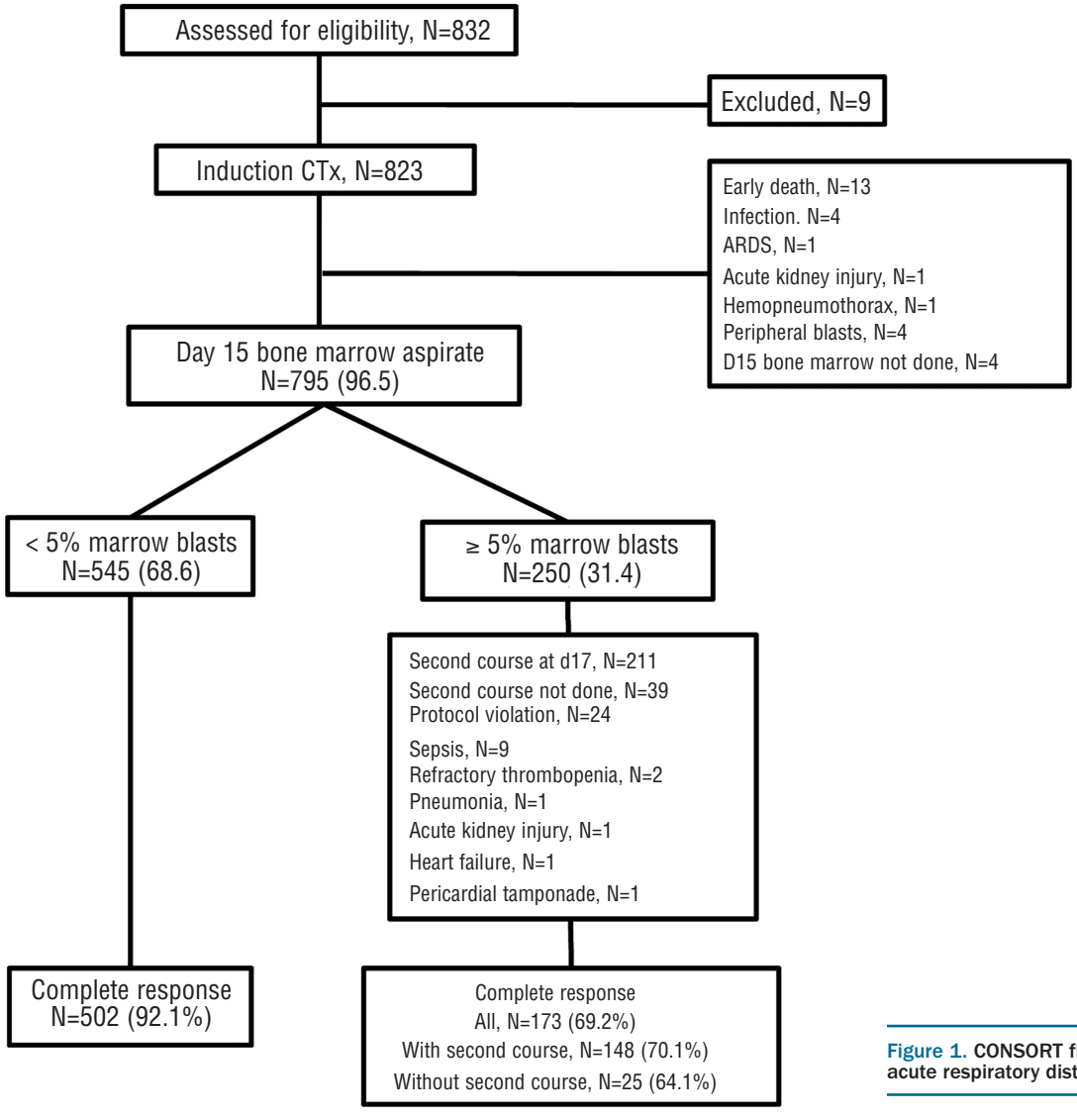

Figure 1. CONSORT flow diagram. ARDS: acute respiratory distress syndrome.

Table 2. Toxicities.

	Day 15 blasts <5%	Day 15 blasts ≥5%	*P*
Time to neutrophil count > 1x10⁹/L (completed, n=630) -days (range)	(n=461)-23 (6-70)	(n=169)-33 (6-76)	<0.0001
Time to platelet count > 20x10⁹/L (completed, n=625) -days (range)	(n=453)-14 (1-56)	(n=172)-26 (1-62)	<0.0001
Time to platelet count > 50x10⁹/L (completed, n=620) -days (range)	(n=454)-21 (1-83)	(n=166)-35 (6-103)	<0.0001
Septicemia (completed, n=681) - n. (%)	(n=483)-66 (13.6)	(n=198)-46 (23.2)	0.003
Bleeding (completed, n=635) - n. (%)	(n=456)-27 (5.9%)	(n=179)-10 (5.6%)	NS
Cardiac event (completed, n=640) - n. (%)	(n=455)- 44 (9.7%)	(n=185)-15 (8.1%)	NS
Mucositis > grade 2 (completed, n=648) - n. (%)	(n=463)-174 (37.5)	(n=185)-70 (37.8)	NS
Median hospitalization duration (completed, n=648)-days (range)	(n=463)-28 (13-82)	(n=185)-39 (13-91)	<0.0001

Table 3. Multivariate analysis of independent risk factors.

	Age	Cytogenetics	d15 blasts	White blood cell count	ECOG
CR, OR [95%CI]	1.03 [1.01-1.05]	2.91 [1.98-4.28]	3.94 [2.54-6.14]	1.00 [0.99-1.01]	1.33 [0.70-2.51]
P	0.01	<0.001	<0.001	0.13	0.38
EFS, OR [95%CI]	1.01 [1.00-1.03]	2.92 [2.18-3.92]	2.35 [1.61-3.41]	1.00 [1.00-1.01]	1.46 [0.86-2.48]
P	0.05	<0.001	<0.001	0.016	0.16
RFS, OR [95%CI]	1.01 [0.99-1.02]	2.46 [1.82-3.32]	1.67 [1.13-2.49]	1.00 [1.00-1.01]	1.34 [0.77-2.32]
P	0.23	<0.001	0.01	0.05	0.29
OS, OR [95%CI]	1.02 [1.00-1.03]	3.46 [2.57-4.65]	1.65 [1.16-2.35]	1.00 [0.99-1.00]	1.21 [0.73-1.99]
P	0.016	<0.001	0.005	0.31	0.46

CR: complete remission; EFS: event-free survival; RFS: relapse-free survival; OS: overall survival; OR: odds ratio; CI: confidence interval. Age and WBC were analyzed as continuous variables; OR for adverse cytogenetics vs. intermediate, d15 blasts < 5% vs. >= 5% and ECOG >1 vs. 0-1 are presented"

Table 4. EFS, RFS and OS according to the distribution of d15 blasts.

	0-4% n=545	5-10% n=57	11-20% n=67	21-50% n=65	>50% n=57	*P*
CR (%)	92	80.7	82.3	66.1	42.1	<0.0001
5-y EFS (%)	48.4±2	32.7±6.3	29.4±5.5	24.4 + 5.3	14±4.6	<0.0001
5-y RFS (%)	52.5±2	40.5±7.4	35.7±6.4	36.9 +7.4	33.3±9.6	<0.05
5-y OS (%)	55.3±2	52.5±6.6	40.1±6	30.7 +5.7	27.6±6.1	<0.05

tory and those of *NPM1* not reported at the time of the study, we cannot determine if early blast clearance is correlated with a specific genotype. However, it has been recently shown that *NPM1* but not *FLT3-ITD* mutations could predict early blast clearance.[22] Furthermore, it will be of interest to determine if early blast clearance has an impact in patients with such favorable genotypes as *NPM1*$^{+}$/*FLT3-ITD*$^{-}$ or *CEBPA*$^{m/m}$ to get a dynamic prognostic scoring since the relapse rate in this subgroup could reach 40-50%. Moreover, early response assessment should be incorporated as an end point in clinical trials to evaluate the anti-leukemic efficacy of treatments. Lastly, failure to achieve an adequate blast clearance at d15 could be considered as an adverse event for EFS and could also be used for stratification of post-remission therapy although a retrospective study from the Eastern Cooperative Oncology Group including 1980 patients (some of them over 60 years of age) enrolled in 6 trials between 1983 to 1993 showed that patients who achieved complete response after one or 2 cycles of induction had a similar prognosis.[23]

The cut-off value of 5% has been a useful tool to identify high-risk patients. In a German study, Heil *et al.* showed that among 305 patients who received idarubicin, standard cytarabine and etoposide, 68% had fewer than 5% d15 blasts, which is in accordance with our results.[24] In the AMLCG 1992 trial, analyses performed for cut-off values of 5%, 10%, 15%, 20%, and 40% showed that respective subgroups differed significantly in all end points.[13] Furthermore, this cut off was validated here in an independent cohort of 152 patients. Whether other methods to assess early response to chemotherapy will be more potent remains to be determined.[25] Our group recently showed that early clearance of peripheral blasts measured by flow cytometry during the first week of induction could be of high predictive value.[26]

Our strategy of the conditional delivery of a second intensified course of chemotherapy is safe, with an overall induction death rate under 5%, and induces a high rate of complete response.[16] Patients with early blast clearance

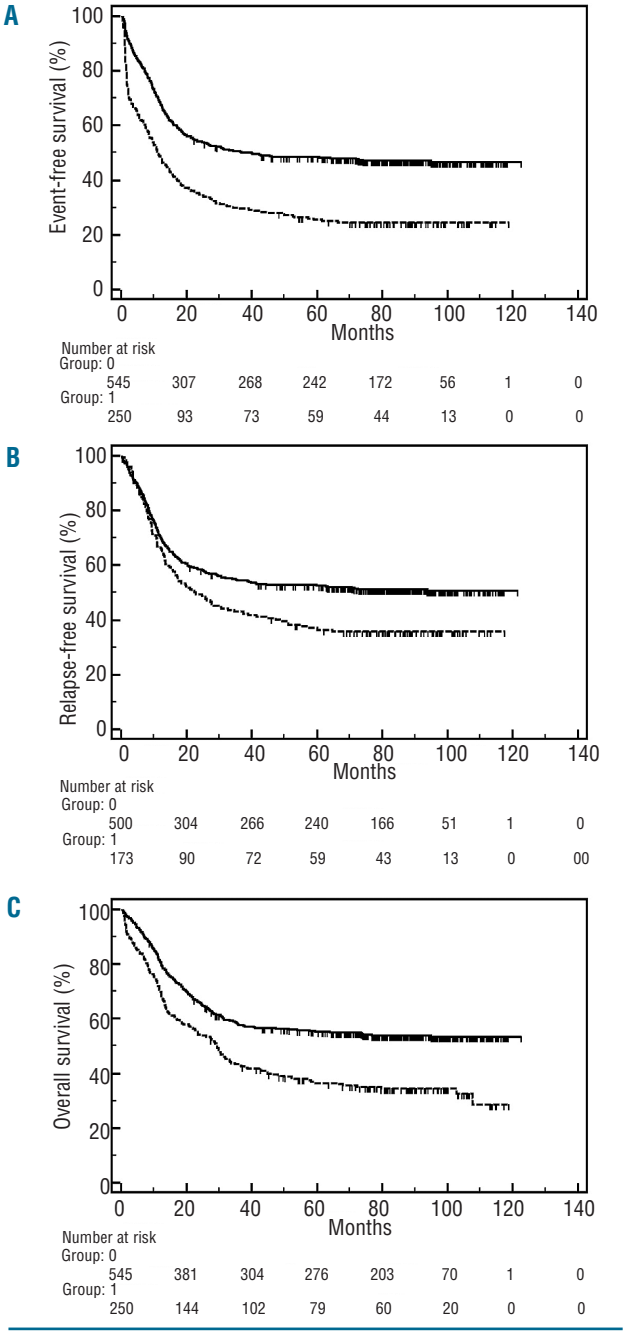

Figure 2. Kaplan-Meier estimates of event-free (A), relapse-free (B) and overall survival (C) according to d15 blasts. Solid line: patients with d15 blasts <5%. Dotted line: patients with ≥5%.

Table 5. Characteristics of 458 AML patients with intermediate-risk cytogenetics.

	All patients n=458	Day 15 marrow blasts <5% n=326	Day 15 marrow blasts ≥5% n=132	P
Median age (range) years	47 (17-61)	47 (17-61)	49 (17-61)	NS
Male gender n. (%)	236 (51.5)	169 (51.8)	67 (50.8)	NS
Performance status* n. (%)				
0-1	408 (89.1)	296 (90.8)	112 (84.9)	NS
2-4	48 (10.5)	28 (8.6)	20 (15.2)	
Median WBC (range) -x10⁹/L	11.4 (0.04-351)	15.5 (0.04-351)	6.6 (0.7-240)	0.0004
Day 15 Marrow blasts				
Median (range)	0 (0-100)	0 (0-4)	20 (5-94)	
0-4 n. (%)	326 (71.2)	326 (100)	0	
5-10 n. (%)	30 (6.6)	0	30 (22.7)	
11-20 n. (%)	36 (7.9)	0	36 (27.3)	
21-50 n. (%)	33 (7.2)	0	33 (25)	
>50 n. (%)	31 (6.8)	0	31 (23.5)	
NA n. (%)	2 (0.4)	0	2 (1.5)	
2nd induction at d15 n. (%)	114 (24.9)	0	114 (86.4)	–
CR – n. (%)	394 (86)	301 (92.3)	93 (70.5)	< 0.0001
Induction failure n. (%)	61 (13.3)	23 (7.1)	38 (28.8)	
Deaths in aplasia	14 (3.1)	5 (1.5)	9 (6.8)	0.0055
Resistant disease	47 (10.3)	18 (5.5)	29 (22)	< 0.0001
AlloSCT n. (%)	101 (22.1)	84 (25.8)	17 (12.9)	0.01

*NA: files mentioned a significant residual leukemic infiltration at d15 but the percentage of blasts was not available; WBC: white blood cell count; alloSCT: allogeneic stem cell transplantation; NS: not significant. * Missing data, n=2. Resistant disease and deaths in aplasia were defined according to the Cheson criteria.[20]*

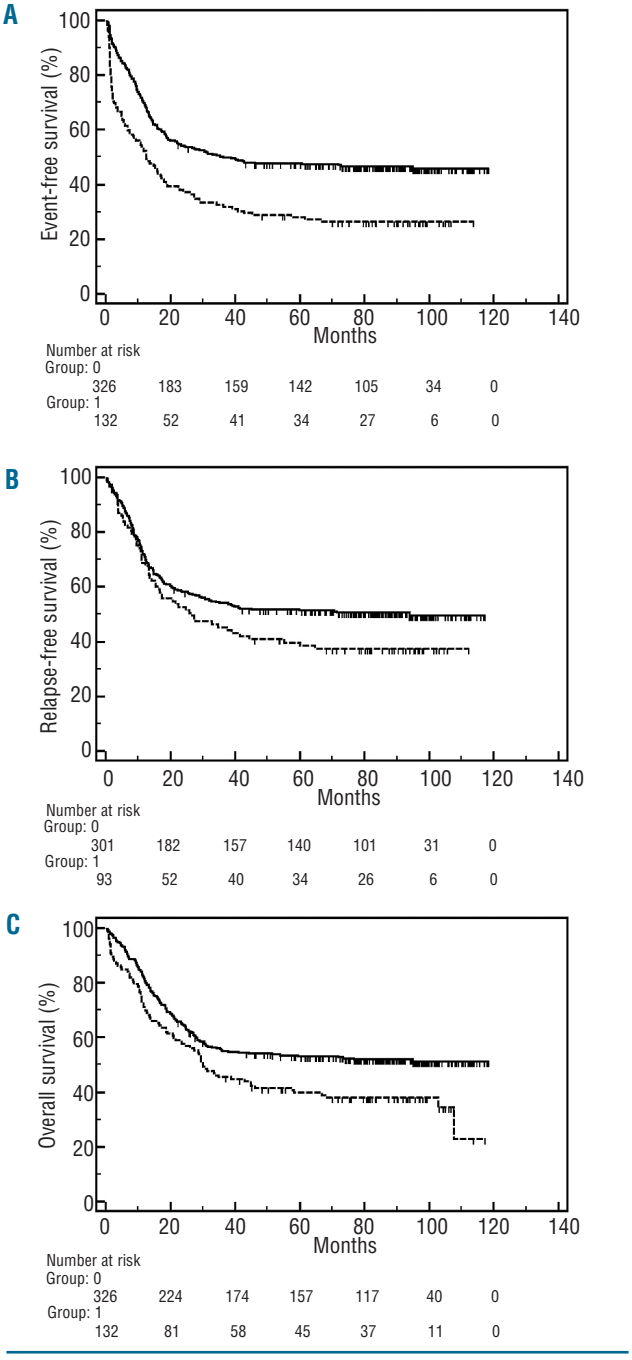

Figure 3. Kaplan-Meier estimates of event-free (A), relapse-free (B) and overall survival (C) according to d15 blasts in patients with intermediate cytogenetic risk. Solid line: patients with d15 blasts <5%. Dotted line: patients with ≥5%.

had a high complete response rate (91.7%), a very low induction death rate (1.8%) and long-term control of the disease (5-year OS 55.3%). In the study of Heil *et al.*, patients with fewer than 5% d15 blasts systematically received a second induction at d20, had a CR rate of 88% and 80-month RFS and OS of 48% and 41%, respectively.[24] The early death rate was 6% which, compared to our results, suggests that delivering a second induction in the phase of aplasia could be detrimental in early responders by increasing the duration of aplasia.[27] Thus, these chemosensitive patients, who account for more than 60% of the patients, likely do not benefit from early intensification both for response and long-term disease control. However, only a randomized study comparing a second early induction course at d16 to nothing in patients with less than 5% blasts would determine if early intensification does or does not improve the outcome of these chemosensitive patients. Moreover, as economic constraints in health care are now a reality, increasing the intensity of induction should be proposed only to a subset of patients who are likely to benefit most from it. We have previously shown that only the control of length of hospital stay may lead to a decrease in induction-related cost in 500 patients included in the LAM-2001 trial.[28] Indeed, an additional course of chemotherapy at d17 significantly increased the median length of hospital stay resulting in a 38% increase in induction-related cost compared to one induction.

Patients with 5% or more blasts at d15 achieved an acceptable CR rate suggesting that early intensification with intermediate-dose cytarabine and anthracycline can salvage a substantial proportion of these patients. It is, however, unknown how many patients could have obtained CR without chemotherapy at d17, especially those with d15 blasts between 5% and 15%.[14] A previous retrospective Italian study had shown that younger patients receiving one course of standard cytarabine and daunorubicin (45 mg/m²) and with more than 22% blasts at d14 had a failure rate of 81%.[29] Conversely, a study from the MD Anderson Cancer Center showed that some patients treated with cytarabine at doses above those used in "3+7" and having a high blast percentage at d14 but achieving a significant decrease at d21, could enter CR without further therapy.[30] In any case, despite a relatively

good CR rate after second induction in our study, the outcome of these patients remained poor with a high rate of relapse, confirming that early evaluation could select patients with a more resistant disease.[13] However, the best regimen to apply between d15 and d20 remains to be determined. The AMLCG study has shown that patients with more than 40% blasts at d16 and/or unfavorable karyotype and/or elevated lactate dehydrogenase level could benefit from high-dose cytarabine with mitoxantrone as compared to a standard second course with CR rates of 65% *versus* 49% and 5-year OS of 25% *versus* 18%, respectively. In our study, of the 211 patients with 5% or more blasts at d15, 70% obtained CR after intermediate-dose cytarabine combined with the same anthracyclin used at first course. The induction death rate in this subgroup was 8%, which is comparable to the study of Heil *et al*. but lower than the AMLCG study (16%).[24]

In the context of both "7+3" and double induction schedule, the persistence of residual bone marrow blasts at d15 identifies a population of high-risk patients independently of cytogenetics. Specific clinical trials should be designed for this subgroup of patients with the aim of establishing a standard of chemotherapy with acceptable toxicity. Conversely, patients with no residual blasts do not seem to benefit from early intensification that could be toxic and cost-ineffective. For these patients, efforts should rather be focused on the consolidation phase to reduce the risk of relapse.

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Authorship and Disclosures

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