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ORIGINAL ARTICLE

Non-infusional vs intravenous consolidation chemotherapy in elderly patients with acute myeloid leukemia: final results of the EORTC-GIMEMA AML-13 randomized phase III trial

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In this trial, acute myeloid leukemia patients (pts) aged 61–80 years received MICE (mitoxantrone, etoposide and cytarabine) induction chemotherapy in combination with different schedules of granulocyte colony-stimulating factor administration. Pts in complete remission were subsequently randomized for two cycles of consolidation therapy: mini-ICE regimen (idarubicin, etoposide and cytarabine) given according to either an intravenous (i.v.) or a 'non-infusional' schedule. Among the 346 pts randomized for the second step, 331 pts received consolidation-1 and 182 consolidation-2. A total of 290 events (255 relapses, 35 deaths in first CR) have been reported. The median follow-up was 4.4 years. No significant differences were detected in terms of disease-free survival (median 9 vs 10.4 months, $P=0.15$, hazard ratio (HR) $=1.18$, 95% confidence interval (CI) 0.94–1.49) – primary end point – and survival (median 15.7 vs 17.8 months, $P=0.19$, HR $=1.17$, 95% CI 0.92–1.50). In the 'non-infusional' arm grade 3–4 vomiting (10 vs 2%; $P=0.001$) and diarrhea (10 vs 4%; $P=0.03$) were higher than in the 'i.v.' arm, whereas time to platelet recovery $>20\times10^9$/l (median: 19 vs 23 days; $P=0.02$) and duration of hospitalization (mean: 15 vs 27 days; $P<0.0001$) was shorter. The 'non-infusional' consolidation regimen resulted in an antileukemic effect similar to the intravenous regimen, which was less myelosuppressive and associated with less hospitalization days.

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Introduction

Results of chemotherapy in elderly patients (pts) with newly diagnosed acute myeloid leukemia (AML) have been disappointing with complete remission (CR) rates of approximately 50% in most series of unselected pts and median durations of disease-free survival (DFS) of less than 1 year.[1]

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There is general agreement that some sort of consolidation treatment should be used in elderly AML pts after reaching CR. Its intensity, however, is an open question. In young pts, the use of intensive consolidation chemotherapy with or without subsequent stem cell transplantation is a general practice following the favorable results reported by several large prospective studies.[2–4] Strategies used for young pts may induce excessive risks when applied in older pts. In most studies, elderly AML pts receive one to three intravenous consolidation courses with reduced dosages, sometimes followed by prolonged maintenance.[5–7] In general, prolonged post-remission therapy does not seem to improve survival compared to short post-remission consisting of 2–3 consolidation courses only.[8] In view of the high relapse rate in older AML adults, we explored a non-infusional post-remission therapy.

Non-infusional treatment might enable treatment on an outpatient basis. The Finnish Leukemia Group published results of a trial[9] using an oral combination of idarubicin, etoposide and thioguanine in pts older than 65 years of age, who were unable to receive standard intravenous (i.v.) therapy. The overall results were not inferior to those usually obtained with different combinations of i.v. therapy. The duration of hospitalization was not different from that of standard regimens, suggesting that an oral regimen may be of value during the consolidation phase, to avoid the need of hospitalization at that stage of treatment.

In this report, we present the final results of the second randomization of the AML-13 trial of the European Organization for Research and Treatment of Cancer (EORTC) and Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) leukemia groups comparing the mini-ICE regimen (idarubicin, cytarabine (Ara-C), etoposide) given intravenously, (control arm) or orally/subcutaneously (s.c.) (experimental arm) in pts who reached CR after standard induction chemotherapy. The aim was to compare the efficacy and toxicity of these two modalities during consolidation therapy. The results of the first randomized question of this trial (value of granulocyte colony-stimulating factor (G-CSF) administered during and/or after the induction chemotherapy) have been published elsewhere.[10] It appeared that the CR rate was significantly higher in pts who received

G-CSF during chemotherapy (58 vs 49%; $P=0.009$), whereas in terms of overall survival (OS) and DFS, no significant differences were observed between the various groups.

Methods

Study design

The AML-13 trial was a randomized phase III study performed in 53 European centers of the EORTC and GIMEMA Leukemia Groups. The final protocol was approved by the EORTC Protocol Review Committee and the Ethical Committee of each participating center. Each patient signed an informed consent before randomization.

Pts 61–80 years of age with previously untreated *de novo* or secondary AML were randomized into four induction arms consisting of mitoxantrone, cytarabine and etoposide (MICE) given either alone or in combination with different schedules of G-CSF administration (Figure 1). Pts entering CR after one or two cycles of MICE were subsequently randomized for two cycles of consolidation treatment consisting of a mini-ICE regimen given according to either an i.v. or a non-infusional schedule. Idarubicin has been chosen because it is the first anthracycline available for both oral and i.v. dosing. To select for equivalent dosages, the bioavailability and pharmocokinetics of the drug in both routes was based on *in vivo* studies performed in one of the participating centers.[11] At selected centers, complete responders 61–70 years with a performance status of 0–1 at the evaluation of consolidation-1 were eligible for a myeloablative chemotherapy followed by re-infusion of autologous peripheral blood stem cells (auto-PBSC) collected at hematologic recovery phase post-consolidation-1.

The main objective of the second randomization was to assess the role of 'non-infusional' mini-ICE as consolidation compared to 'i.v.' mini-ICE. The primary end point was DFS. Secondary end points included duration of remission, incidence of death in CR, duration of survival, toxicity, number of days to hematopoietic recovery, duration of hospitalization and duration of i.v. antibiotics.

Patients

Pts 61–80 years of age with a morphologically confirmed diagnosis of either untreated *de novo* or secondary AML, except for acute promyelocytic leukemia, with $\geqslant 30\%$ blast cells in the bone marrow were eligible for first randomization. Blast crisis of chronic myeloid leukemia and leukemias supervening after other myeloproliferative diseases were excluded. Prior treatment for secondary myelodysplasia with cytarabine (doses <100 mg/m^2) administered more than 6 weeks before registration was allowed. Eligibility for second randomization included: first CR (CR1) after induction; WHO performance status of 0–2; absence of severe cardiac, pulmonary, neurologic and metabolic disease; adequate liver and renal function tests; absence of active infection; and HIV negativity. Informed consent in accordance with local institutional guidelines and federal regulations was required of all pts. Eligibility for myeloablative chemotherapy with auto-PBSC support as second consolidation course, required in addition age 61–70 years and WHO performance status of 0 or 1 at evaluation of consolidation-1.

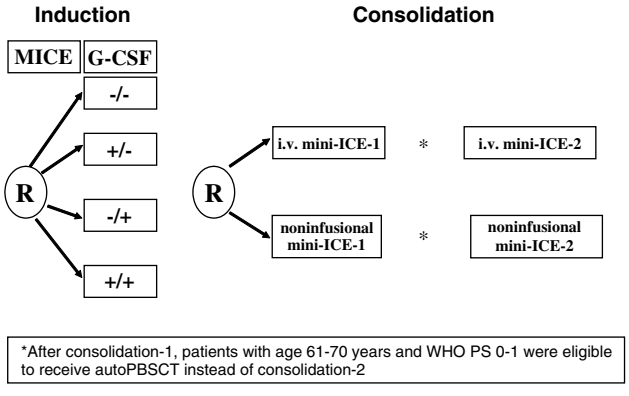

Figure 1 AML-13 schema.

Treatment

Pts received 1 or 2 remission–induction cycles of an i.v. MICE regimen (mitoxantrone 7 mg/m^2 on days 1, 3 and 5; etoposide 100 mg/m^2 on days 1–3; Ara-C 100 mg/m^2 continuous infusion on days 1–7). In a first step, pts have been randomized to either Lenograstim (Granocyte®) 150 μg/m^2 on days 1–7, days 8–28, days 1–28 or none. Pts reaching CR were randomized in a second step for two cycles of consolidation consisting of either 'i.v.' mini-ICE (idarubicin 8 mg/m^2 i.v. bolus injection on days 1, 3 and 5; etoposide 100 mg/m^2 1 h i.v. infusion on days 1–3; Ara-C 100 mg/m^2 continuous infusion on days 1–5) or 'non-infusional' mini-ICE (idarubicin 20 mg/m^2 orally (after breakfast), in capsules of 5, 10 or 25 mg, on days 1, 3 and 5; etoposide 100 mg/m^2 orally, twice daily (after breakfast and dinner), on days 1–3; Ara-C 50 mg/m^2 s.c., twice daily, on days 1–5). Oral idarubicin (Zavedos®) was supplied by Pfizer bv, Rivium Westlaan 142, LD Capelle a/d IJssel, The Netherlands. Drug delivery was performed by each local center using locally developed patient friendly forms.

Details of the treatment and results of those pts receiving high-dose chemotherapy (BCNU (*N*,*N*-bis[2-chloroethyl]-*N*-nitrosourea), amsacrine, VP-16 and cytosine arabinoside (BAVC) conditioning regimen) with auto-PBSC support were presented in part elsewhere.[12] Only 18 centers out of 53 chose to perform auto-PBSCT after consolidation.

Criteria of evaluation

The Cancer and Leukemia Group B criteria for response to treatment and relapse were used.[13] International System for Human Cytogenetic Nomenclature was applied for cytogenetic classification.[14] Abnormalities 16q(22) and t(8;21) were considered favorable risk abnormalities, independent of whether other abnormalities were present or not. Those with a normal karyotype or with –Y only were classified as intermediate risk. Those with $-5/5q-$ or $-7/7q-$ or with complex abnormalities (>3 abnormalities) were considered unfavorable abnormalities. Pts with other abnormalities were pooled into a separate group ('other'). Regarding morphology, the French–American–British cytological classification has been used.[15,16]

Toxicity was evaluated according to the National Cancer Institute (NCI) common toxicity scale. A harvest was considered successful if $\geqslant 2\times 10^6$ CD34$^+$ cells/kg could be collected.

Statistical methods

Randomization was performed centrally (EORTC Data Center), with stratification for center, induction (MICE and no G-CSF vs MICE and G-CSF days 1–7 vs MICE and G-CSF days 7–28 vs MICE and G-CSF days 1–28), cytogenetics (good vs intermediate vs poor vs other vs unknown/failure), response to first induction

course, using the minimization technique. DFS was calculated from the second randomization until the date of first relapse or death in first CR or last date of follow-up (censored observations). Duration of survival was calculated from second randomization until date of death (whatever the cause) or last date known to be alive (censored observations). Duration of recovery was defined as the time from start of consolidation until polymorphonuclear cells or platelet recovery; pts without recovery were censored at day 90.

The aim of the second randomization, 'non-infusional' vs 'i.v.' administration of mini-ICE was to detect a difference between the two arms in terms of DFS (main end point) and survival. The median DFS in the control group ('i.v.' arm) was expected to be 10 months and the 2-year DFS rate of approximately 20%. It was considered that a 10% loss (10 vs 20%) or a 12% increase (20 vs 32%) in the 2-year DFS rate would be of clinical importance. This would translate into a 3-month decrease or a 4.3 month increase in median DFS between the 'non-infusional' vs 'i.v.' arm, corresponding to a hazard ratio (HR) of 1.43 or 0.7. A total of 255 events (relapses or deaths) were required for detecting a treatment difference with an 80% statistical power (two-tailed log-rank test, $\alpha = 5\%$).

Actuarial curves were calculated according to the Kaplan–Meier technique.[17] The standard errors (s.e.) of the estimates were computed using the Greenwood formula.[17] The estimates of the cumulative incidences of relapse and of death in CR1, and their s.e., were obtained by considering death in CR1 and relapse as competing risks.[18] The differences between Kaplan–Meier curves were compared by using the two-tailed long-rank test,[17] whereas for the cumulative incidences the Gray test was used.[18] The Cox's proportional hazards model has been employed to obtain the estimate and the 95% confidence interval (CI) of the HR, ratio of the instantaneous event rate in the 'non-infusional' vs the one in the 'i.v.' arm.[17] The main analyses regarding the treatment efficacy was based on all pts randomized, the intent-to-treat (ITT) principle being followed. Sensitivity analyses were performed by excluding either pts who did not start treatment allocated by randomization or censoring the follow-up at time of autoPBSCT. The duration of hospitalization and of i.v. antibiotics, and the grade (0, 1–2, 3–4) of infections were compared using the Wilcoxon test.[17] Grade 3–4 toxicities were compared using the Fisher exact two-tailed test. The Bonferroni adjustment for multiple comparisons (four in total: nausea, vomiting, diarrhea and infection) indicate that $P \leqslant 0.0125$ should be considered as significant and $0.0125 < P \leqslant 0.05$ as borderline significant. The SAS 8.2 software (SAS Institute Inc., Cary, NC, USA) has been used for the statistical analyses.

Results

A total of 757 pts with either *de novo* (78%) or sAML (22%) from 53 institutions were enrolled in this study between December 1995 and October 2001. In February 2001, the randomization for the G-CSF question was stopped, as the study reached required number of pts. Thereafter, all pts received MICE induction alone, and randomization of consolidation continued, in order to reach the number of pts for the second question of the trial. For entire group of pts the median age was 67 years. Four hundred-five pts (54%) reached CR after one or two cycles for induction.

A total of 346 pts were randomized for the second step. Overall, the median age was 67 years (range 60–79). The baseline characteristics and induction treatments were well balanced in both groups (Table 1). The median WBC was 7.7 ('i.v.') vs 6.2×10^9/l ('non-infusional').

Table 1 Patient characteristics by treatment arm

	'i.v.' mini-ICE (n = 172) No. (%)	*'Non-infusional' mini-ICE (n = 174) No. (%)*
Age at registration		
61 to <70	121 (70)	117 (67)
⩾70	51 (30)	57 (33)
Sex		
Male	90 (52)	85 (49)
Female	81 (47)	87 (50)
Not recorded	1 (1)	2 (1)
WHO PS at registration		
0	81 (47)	96 (55)
1	76 (44)	69 (40)
2	15 (9)	9 (5)
Type of AML		
De novo	146 (85)	145 (83)
Secondary	26 (15)	29 (17)
FAB subtype		
M0	10 (6)	12 (6)
M1	24 (13)	44 (25)
M2	58 (34)	49 (28)
M4	31 (18)	31 (18)
M5	32 (19)	27 (16)
M6	7 (4)	3 (2)
M7	2 (1)	2 (1)
Missing/unknown	8 (5)	6 (4)
WBC ($\times 10^9$/l) at registration		
<25	123 (72)	120 (69)
25 to <100	34 (20)	33 (19)
⩾100	14 (8)	17 (10)
Not recorded	1 (1)	4 (2)
Cytogenetics		
Good	7 (4)	4 (2)
Intermediate	48 (28)	59 (34)
Poor	22 (13)	25 (14)
Other	20 (12)	13 (7)
Failure	36 (21)	33 (19)
Unknown/ND	36 (23)	35 (20)
Induction treatment		
MICE control	37 (22)	38 (22)
MICE+G-CSF d1–7	37 (22)	38 (22)
MICE+G-CSF d8–28	42 (24)	41 (24)
MICE+G-CSF d1–28	48 (28)	50 (29)
MICE non-randomized	8 (5)	7 (4)
Response to first induction course		
CR	162 (94)	160 (92)
No CR	10 (6)	14 (8)

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; FAB, French–American–British; G-CSF, granulocyte colony-stimulating factor; i.v., intravenously; MICE, mitoxantrone, etoposide and cytarabine; ND, not determined; WBC, white blood corpuscles; WHO, World Health Organization.

Treatment compliance

Among the 346 pts randomized, 15 (six 'i.v.' vs nine 'non-infusional'), did not start the assigned treatment owing to ineligibility ($N = 7$), early relapse ($N = 2$), too high induction toxicity ($N = 2$), protocol violation ($N = 3$), treatment refusal

($N=1$). Among the remaining 331 pts, who received the consolidation-1 course (166 'i.v.' vs 165 'non-infusional'), 182 (89 vs 93) received a second course of consolidation, 35 (22 vs 13) an autoPBSCT and 114 (55 vs 59) went off-study for different reasons, essentially owing to toxicity/treatment refusal ($N=77$) or relapse ($N=37$). Among 61 (33 'i.v.' vs 28 'non-infusional') pts who received G-CSF for mobilization after recovery from consolidation-1, stem cell harvest was performed in 54 pts, of whom, 40 (25 'i.v.' vs 15 'non-infusional') had an adequate harvest. Among these, five pts (three 'i.v.' vs two 'non-infusional' pts) have not been transplanted: three relapsed (two vs one) and two (one vs one) refused further treatment.

In the 'non-infusional' arm less pts (73%) received consolidation-1 course without modifications in the dosage/scheduling of the study drugs as compared to the 'i.v.' arm (95%) ($P<0.001$). The drug delivery violations were mostly associated with the twice-daily scheduling of oral etoposide and/or, to a lesser extent, subcutaneous cytarabine or oral idarubicin (Table 2). A similar trend was evident during consolidation-2.

Toxicity

The spectrum of maximum non-hematologic toxicity during both consolidation cycles was quite similar in the two randomized arms (Table 3). However, severe (NCI grade 3–4) gastrointestinal toxicity occurred more frequently in pts treated with the 'non-infusional' regimen as compared to the 'i.v.' consolidation regimen, regardless of the administration of prophylactic antiemetics: nausea 9 vs 4% ($P=0.08$), vomiting 10 vs 2% ($P=0.001$), diarrhea 10 vs 4% ($P=0.03$). In contrast, the grade of infection was higher, in mean, the 'i.v.' arm as compared with the 'non-infusional' arm ($P=0.01$), whereas grade 3–4 of infections were not significantly different: 26 vs 20% ($P=0.25$). More pts required i.v. antibiotics in the 'i.v.' than in 'non-infusional' mini-ICE: 42 vs 26% during consolidation-1, and 48 vs 39% for the consolidation-2. The number of days of i.v. antibiotics was also longer in the 'i.v.' mini-ICE: 10 vs 7 days ($P<0.001$) for consolidation-1 and 14 vs 6 days ($P<0.001$) for consolidation-2.

Duration of pancytopenia and duration of hospitalization

Platelet recovery ($>20\times10^9$/l) was faster in the 'non-infusional' arm after both consolidation-1 (median: 19 vs 23 days; $P=0.02$) and consolidation-2 (median: 21 vs 25 days; $P=0.003$). The same trend was observed regarding neutrophil recovery ($>0.5\times10^9$/l) after the consolidation-1 (median: 23 vs 26 days;

Table 2 Dose modifications and dosages of the three drugs administered during each course by treatment arm

	Consolidation-1		*Consolidation-2*	
	'i.v.' mini-ICE (n=166) No. (%)	*'Non-infusional' mini-ICE (n=165) No. (%)*	*'i.v.' mini-ICE (n=89) No. (%)*	*'Non-infusional' mini-ICE (n=93) No. (%)*
Treatment modified				
No	158 (95)	121 (73)	82 (92)	68 (73)
Daily dosages	7 (4)	42 (26)	6 (7)	22 (24)
Schedule	1 (1)	1 (1)	1 (1)	3 (3)
Both	0 (0)	1 (1)	0 (0)	0 (0)
Reason of modification				
Unknown	0 (0)	3 (2)	0 (0)	1 (1)
Non-hematological toxicity	1 (1)	0 (0)	3 (3)	2 (2)
Non compliance of patient	0 (0)	1 (1)	1 (1)	1 (1)
Mistake[a]	5 (3)	32 (19)	1 (1)	18 (19)
Other	2 (1)	8 (5)	2 (2)	3 (3)
Idarubicin % dose given				
30 to <50	0 (0)	0 (0)	1 (1)	2 (2)
50 to <70	2 (1)	0 (0)	2 (2)	2 (2)
70 to <90	4 (2)	9 (5)	2 (2)	4 (4)
90 to <110	159 (96)	152 (92)	83 (93)	84 (90)
⩾110	1 (1)	4 (2)	1 (1)	1 (1)
Ara-C % dose given				
20 to <50	0 (0)	3 (2)	0 (0)	1 (1)
50 to <70	0 (0)	5 (3)	0 (0)	3 (3)
70 to <90	3 (2)	3 (2)	1 (1)	3 (3)
90 to <110	161 (97)	148 (90)	86 (97)	83 (89)
⩾110	2 (1)	6 (4)	2 (2)	3 (3)
Etoposide % dose given				
20 to <50	0 (0)	7 (4)	0 (0)	5 (5)
50 to <70	1 (1)	9 (5)	2 (2)	5 (5)
70 to <90	2 (1)	8 (5)	0 (1)	4 (4)
90 to <110	163 (98)	138 (84)	87 (98)	77 (83)
⩾110	0 (0)	3 (2)	0 (0)	2 (2)

Abbreviations: Ara-C, cytarabine; ICE, idarubicin, etoposide and cytarabine; i.v., intravenously.
[a]Such mistakes were due to either a misunderstanding of the protocol, particularly on the schedule of oral etoposide (for instance, 50 mg/m^2/day were administered instead of 50 mg/m^2 every 12 h), or due to the availability of oral idarubicin in capsule of 5, 10 and 20 mg, which led to under or over-dosages >10%, as an exact dose adjustment according to body surface area could not be performed properly.

Table 3 Maximum side effects during/after consolidation-1 and -2 by treatment arm in the per-protocol treatment population

Type	*'i.v.' mini-ICE* (n = *166*)		*'Non-infusional' mini-ICE* (n = *165*)	
	Grades 1–4 No. (%)	*Grades 3–4 No. (%)*	*Grades 1–4 No. (%)*	*Grades 3–4 No. (%)*
Gastrointestinal				
Nausea	98 (59)	7 (4)	107 (65)	15 (9)
Vomiting	69 (42)	3 (2)	80 (48)	17 (10)
Diarrhea	65 (39)	6 (4)	75 (45)	16 (10)
Stomatitis oral	75 (45)	8 (5)	64 (39)	8 (5)
Body as a whole				
Infection	108 (65)	43 (26)	84 (50)	33 (20)
Headache	26 (16)	1 (1)	21 (13)	0 (0)
Other flu-like	7 (5)	1 (1)	11 (7)	1 (1)
Rigors/chills	21 (13)	1 (1)	10 (6)	0 (0)
Bone pain	10 (6)	1 (1)	9 (6)	0 (0)
Hematological				
Hemorrhage	55 (33)	2 (1)	48 (29)	4 (2)
Prothrombin time	5 (3)	0 (0)	12 (7)	0 (0)
Fibrinogen	7 (4)	0 (0)	6 (4)	0 (0)
Hepatic				
Any	34 (20)	9 (5)	33 (20)	10 (6)
Cardiovascular				
Edema	15 (9)	0 (0)	22 (13)	1 (1)
Hypotension	17 (10)	3 (2)	19 (12)	6 (4)
Dysrhythmias	13 (8)	1 (1)	13 (8)	4 (2)
Cardiovascular function overall	4 (4)	1 (1)	9 (5)	3 (2)
Genitourinary				
Any	18 (11)	0 (1)	19 (12)	1 (1)
Skin				
Rash/itch	34 (20)	2 (1)	18 (11)	1 (1)

Abbreviations: ICE, idarubicin, etoposide and cytarabine; i.v., intravenously.

$P = 0.09$) and after consolidation-2 (median: 24 vs 26 days; $P = 0.25$).

Pts in the 'non-infusional' arm had a significantly shorter duration of hospitalization as compared to those in the 'i.v.' arm during consolidation-1 (mean: 15 vs 27 days; $P < 0.0001$), consolidation-2 (mean: 13 vs 26 days; $P < 0.0001$) and during both (mean: 24 vs 51 days; $P < 0.0001$).

DFS and survival

The median follow-up was 4.4 years (range 0–7 years). Out of the 346 pts randomized, on an ITT basis, including the 35 pts who underwent bone marrow transplantation and the 15 pts randomized, but not treated, a total of 290 events have been reported: 255 relapses (136 'non-infusional' arm vs 119 'i.v.' arm) and 35 deaths in CR1 (15 vs 20); a total of 264 pts (138 vs 126) have died.

Regarding DFS, the primary end point of this study, the difference between the two treatment groups was not significant ($P = 0.15$), the HR was 1.18, 95% CI 0.94–1.49, the median estimate was 9 months ('non-infusional') vs 10.4 months ('i.v.') (Figure 2). The 3-year DFS rate was 13% (s.e. = 3%) vs 21% (s.e. = 3%). The 3-year cumulative incidence of relapse was 79% (s.e. = 3%) in the 'non-infusional' arm vs 67% (s.e. = 4%) in the 'i.v.' ($P = 0.06$), and the 3-year cumulative incidence of death in CR1 was 8% (s.e. = 2%) and 12% (s.e. = 3%) respectively ($P = 0.33$).

Using the Cox model, the treatment comparison of the two arms in terms of DFS adjusted for cytogenetics (good, intermediate, other, poor, failure and unknown), type of disease (*de novo* vs secondary AML) and sex, remained unchanged: HR = 1.17 (95% CI 0.93–1.48), $P = 0.19$. Other variables had no prognostic impact. Treatment adjustment for the dose of etoposide ($<$ vs $\geqslant$90% of the required dose) had no real impact on the comparison (data not shown).

Similarly, there was no significant ($P = 0.19$) difference in the OS, the HR was 1.17 (95% CI 0.92–1.50), median was 15.7 months in the 'non-infusional' vs 17.8 months in the 'i.v.' arm (Figure 3). The 3-year survival rates were 25% (s.e. = 3%) and 30% (s.e. = 4%) respectively. Using the Cox model, the treatment comparison adjusted for cytogenetics, type of disease and sex, yielded a HR of 1.12 (95% CI 0.88–1.44), $P = 0.35$.

Among 35 pts who were transplanted in CR1, 22 relapsed and five died in CR1. By censoring the follow-up at time of transplantation, treatment comparisons in terms of DFS and survival remained essentially unchanged (data not shown). The exclusion of 15 pts who did not start the randomized treatment had no impact on treatment comparisons either.

For the 405 pts who reached CR, median DFS was 9 months and the 3-year DFS rate was 18%, and for survival from CR, it was 17.5 months and 27% respectively. For all 757 pts registered in this study median survival was 9 months and the 3-year survival rate 17%.

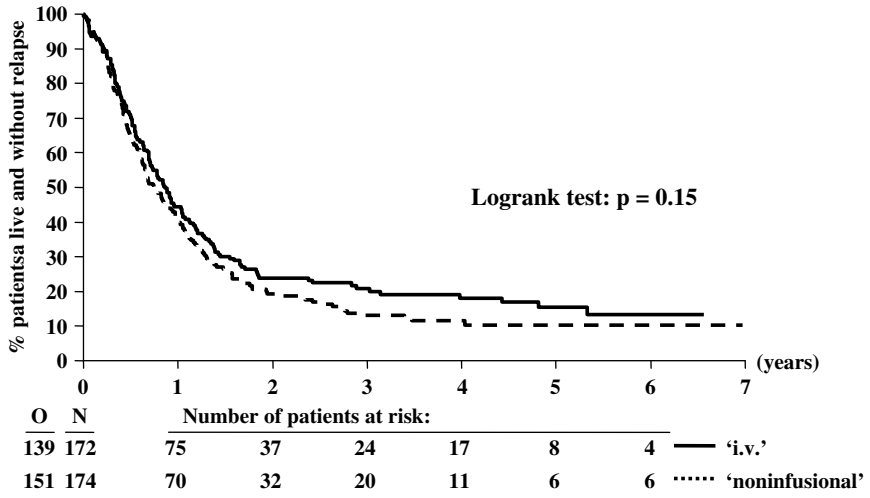

Figure 2 DFS by treatment arm. *N* = Number of patients in each treatment group. *O* = Observed number of events (relapse or death in CR1).

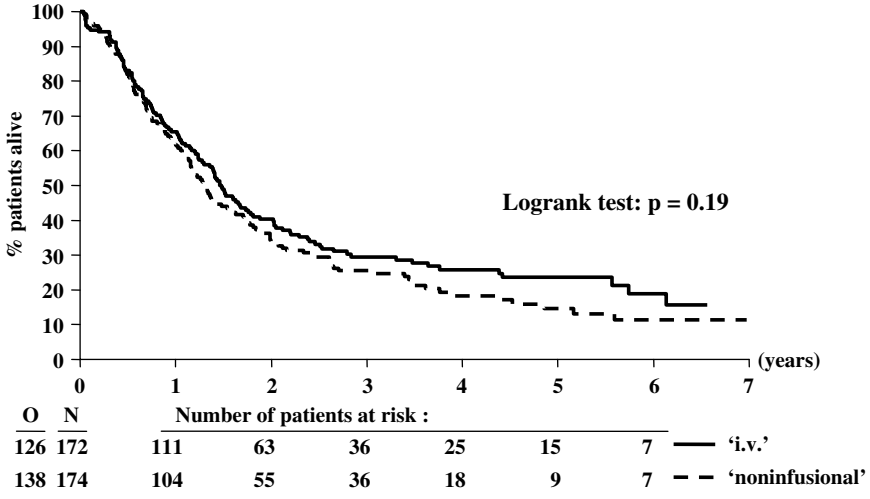

Figure 3 Duration of survival by treatment arm. *N* = Number of patients in each treatment group. *O* = Observed number of deaths.

Discussion

AML is predominantly a disease of the elderly; the median age at presentation is 64 years, and 60% of all cases are over 60 years.[19–21] AML is a dismal diagnosis in older pts because most pts are not fit enough for intensive therapy. Usually, therapy results in low CR rates, high treatment-related toxicities, short relapse-free and OS.[22] The optimal management strategy is a controversial issue with opinions frequently polarized between low and high-intensity remission induction. Areas of controversy include the importance of consolidation and maintenance chemotherapy as well.

This randomized phase III trial was designed for medically fit pts 61–80 years of age with untreated *de novo* or secondary AML. The results of the first randomized question have been published elsewhere.[10]

Pts entering CR after 1 or 2 cycles of MICE were randomized subsequently for two cycles with mini-ICE for consolidation given according to either an i.v. or an oral/subcutaneous schedule. The main aim was to detect a difference in median DFS from 7 to 10 months between the two treatment arms, and also to determine whether or not consolidation could be given on an outpatient basis with the intention to improve quality of life of these pts.

Our data indicate that a 'non-infusional' mini-ICE consolidation regimen is associated with an antileukemic effect not significantly different from that provided by the standard i.v. schedule. The 3-year DFS rates were similar in the 'non-infusional' and 'i.v.' arms, leading to comparable median estimates (9 vs 10.4 months) and an estimated HR close to one. Despite a total of 290 events reported in this study, allowing the detection with an 85% power of a treatment difference in DFS, which was considered clinically meaningful, we were unable to detect a statistical difference. Survival was not significantly different either. It is noteworthy that DSF and survival results in both groups of the present study were comparable to those reported for other intensive treatment regimens in elderly AML pts.[2–9,22] This holds also true when considering all pts who reached CR or all pts registered.

The toxicity profiles of the two regimens were similar, with the exception of a higher frequency of gastrointestinal side effects (nausea, vomiting, diarrhea) associated with the administration of 'noninfusional' regimen.

Decreased compliance to the fractionated daily dosing of oral etoposide and idarubicin, and subcutaneous cytarabine may be expected for pts randomized to the 'non-infusional' arm, since the supervision of the self administered non-i.v. schedule was less strict than in the intravenous schedule. Roughly 10% of pts showed a reduced compliance with the regular twice-daily intake of oral etoposide. Such reductions occurred also owing to a misunderstanding of the protocol by the investigators: one administration instead of two for the drugs, which were scheduled twice daily (etoposide or Ara-C) rather than once daily (idarubicin).

Profound thrombocytopenia and neutropenia generally lasted more than 2 weeks in each treatment arm. The duration of thrombocytopenia was significantly shorter (3–4 days) after the 'noninfusional' regimen, whereas the reduction in duration of neutropenia (2–3 days) was borderline significant. Given its less intensive myelosuppressive effects it is not surprising that the 'non-infusional' regimen was associated with a reduced mean grade of infectious complications and less mean number of days of i.v. antibiotics (reduction of 3 days during consolidation-1 and of 8 days during consolidation-2).

In our study, the duration of hospitalization was significantly shorter (by 12–13 days) in pts receiving the 'non-infusional' formulation of the mini-ICE consolidation on an outpatient basis, as compared to those randomized to the i.v. mini-ICE.

In our trial, we could not detect a significant difference in terms of DFS between the i.v. and non-infusional consolidation regimens despite we had adequately powered the trial. The non-infusional regimen required less hospitalization days as it was scheduled to be administered at home, unless complications were noticed. It also required less i.v. antibiotics, as the observed grades of infection were lower. The duration of myelosuppresion, particularly thrombocytopenia, seemed also shorter in the noninfusional arm as compared with the i.v. arm, although this outcome might had been influenced by lower treatment applicability. Further modifications of this non-infusional regimen (e.g. once daily dosing, better antiemetic support), may probably improve compliance and decrease the side effects, particularly nausea-vomiting, of the treated pts.

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Supplementary Information accompanies the paper on the Leukemia website (http://www.nature.com/leu)