Impact of post-remission therapy in patients aged 65-70 years with *de novo* acute myeloid leukemia: a comparison of two concomitant randomized ALFA trials with overlapping age inclusion criteria

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ABSTRACT

Background
There is no standard post-remission therapy in older patients with acute myeloid leukemia.

Design and Methods
From 1999 to 2006, the Acute Leukemia French Association group ran two concurrent randomized trials with overlapping inclusion criteria for patients aged 65 to 70 with acute myeloid leukemia, with different post-remission strategies: two intensive courses in the 9801 trial, one intensive course or six outpatient courses in the 9803 trial. We analyzed the outcome of these patients *per* protocol and *per* post-remission therapy.

Results
Two hundred and eleven patients aged 65 to 70 years with *de novo* acute myeloid leukemia were enrolled in trial 9801 (n=76) or 9803 (n=135). The patients in the two trials had comparable white blood cell counts (P=0.3), cytogenetics (P=0.49), and complete remission rates (70% and 57%, respectively; P=0.17). Overall survival was identical in both trials (32% and 34% at 2 years, respectively; P=0.71). Overall survival after complete remission was identical in the 103 of 130 patients who received the planned post-remission courses (n=44 with two intensive courses, n=28 with one intensive course, n=31 with six outpatient courses; 41%, 55%, and 58% at 2 years, respectively; P=0.34). Even in patients with favorable or normal karyotype (n=97), overall survival from complete remission was not improved by more intensive post-remission therapy.

Conclusions
In patients aged 65 to 70 years with *de novo* acute myeloid leukemia in complete remission after standard intensive induction chemotherapy, there is no apparent benefit from intensive post-remission therapy. *(ClinicalTrials.gov Identifiers: NCT00931138 and NCT00363025)*

Key words: acute myeloid leukemia, post-remission therapy, older patients.

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Introduction

Acute myeloid leukemia (AML) frequently occurs in older patients, with a poor prognosis due to more resistant disease and greater frailty of such patients.[1] Patients likely to benefit from intensive chemotherapy combining standard doses of cytarabine arabinoside with an anthracycline ("7+3" regimen) can be identified by various scores,[2-4] including a proposed decision index derived by our group.[5] Age, cytogenetics, white blood cell count, antecedent hematologic disorders, performance status, and comorbidities are the main factors which are taken into consideration for decision-making. In selected patients, standard intensive induction yields complete remission rates around 50%.[6] Induction dose escalation does not improve outcome after 65 years of age.[7] Once complete remission has been reached, there is no well-established standard for post-remission therapy in older AML patients. Randomized studies from the 1990s failed to demonstrate any benefit of intensification either by increasing the doses,[8] number of courses,[9] or number of chemotherapy agents, except in highly selected patients.[10] Since those studies were performed, the prognosis of older AML patients treated intensively might have improved with progresses in supportive care,[11] warranting a reappraisal of the potential benefit associated with intensive post-remission therapy.

The Acute Leukemia French Association (ALFA) completed a trial in AML patients aged over 65 years with *de novo* or secondary AML (ALFA-9803)[12] in which patients in first complete remission were randomized between two post-remission strategies, an intensive regimen delivered in the hospital, and an outpatient strategy consisting of six courses of single-dose anthracycline combined with subcutaneous cytarabine arabinoside. Although this study was the first to demonstrate an overall survival advantage in favor of the outpatient approach, this conclusion was weakened by the fact that the "intensive" arm consisted of a single "3+7" reinduction course, leaving open the possibility that a more intensive post-remission strategy could have been more efficient, especially in younger patients close to 65 years of age. Concomitantly, the ALFA initiated another trial, referred to as ALFA-9801 and designed for patients aged 50 to 70 years old with *de novo* AML.[13] In this trial, patients in complete remission received a more intensive post-remission regimen with two courses of intermediate-dose cytarabine arabinoside, combined with anthracyclines.[13] The age overlap of 65-70 years in the inclusion criteria for these two concomitant trials provided the opportunity to compare different intensities of post-remission treatment in older patients with *de novo* AML in first complete remission.

Design and Methods

Patients and eligibility criteria

The ALFA-9801 and ALFA-9803 trials enrolled 478 and 416 patients from 01/2000 to 10/2006 and from 10/1999 to 03/2006, respectively, in the same 24 centers. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The 9801 and 9803 trials were approved by the ethic committees of Saint-Louis and La Pitié-Salpétrière Hospitals respectively, and were registered at *www.clinicaltrials.gov* under identifiers NCT00931138 and NCT00363025, respectively. The eligibility criteria were age over 64 years and a previously untreated AML (marrow blasts ≥ 30%, *de novo* or secondary to myelodysplastic syndrome) for the 9803 trial,[12] and an age comprised

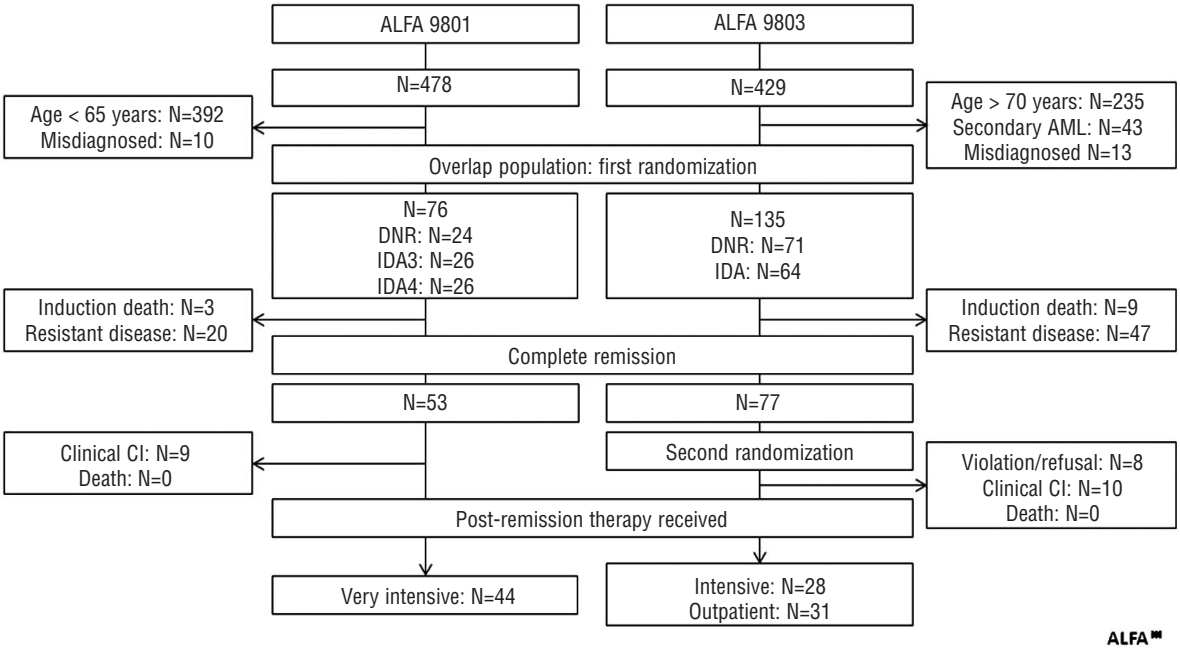


Figure 1. CONSORT diagram of the overlap study population. CI: contraindication; Tx: treatment.

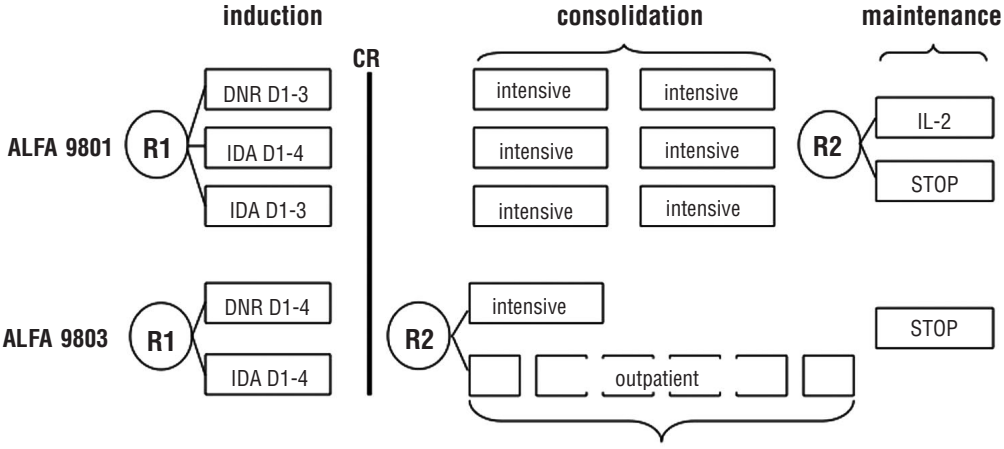


Figure 2. Treatment plans for trials 9801 and 9803. R1: first randomization; R2: second randomization; IL-2: interleukin-2; DNR: daunorubicin; IDA: idarubicin; CR: complete remission.

between 50 and 70 years with a diagnosis of *de novo* AML (marrow blasts ≥ 30%) in the 9801 trial.[13] Exclusion criteria were similar in the two trials: (i) acute promyelocytic leukemia, therapy-related AML; (ii) severe comorbidity (grade 3-4 infection, symptomatic myocardial, cardiac, hepatic, renal, neuro-psychiatric, or auto-immune condition); and (iii) performance status score greater than 3. Only patients aged 65 to 70 years with *de novo* AML were analyzed in the present study. The CONSORT diagram of the study population is recapitulated in Figure 1.

Treatments

The treatment schemes of both trials are summarized in Figure 2 and detailed in the reports by Gardin *et al.*[12] and Pautas *et al.*[13] In both trials, patients were randomized front-line (first randomization) to receive either daunorubicin or idarubicin throughout the study. In the 9803 trial, induction chemotherapy consisted of daunorubicin 45 mg/m^2/day intravenously or idarubicin 9 mg/m^2/day intravenously for 4 days with cytarabine arabinoside 200 mg/m^2/day by continuous intravenous infusion for 7 days. Lenograstim 263 μg/day was administered intravenously from day 9 until neutrophil recovery. In the 9801 trial, induction consisted of daunorubicin 80 mg/m^2/day intravenously for 4 days or idarubicin 12 mg/m^2/day intravenously for 3 days or idarubicin at the same daily dose for 4 days, with cytarabine arabinoside 200 mg/m^2/day administered by continuous intravenous infusion for 7 days. In this trial, patients did not receive granulocyte colony-stimulating factor (G-CSF) prophylaxis. In both trials, a salvage course was planned for patients with persistent leukemia on day 21. In the 9803 trial, salvage therapy consisted of cytarabine arabinoside 500 mg/m^2/12 h by intravenous bolus (days 1-3) with mitoxantrone 12 mg/m^2/day for 2 days (days 3 and 4), while in the 9801 trial the salvage therapy consisted of cytarabine arabinoside 1000 mg/m^2/12 h by intravenous bolus (days 1-4) with mitoxantrone 12 mg/m^2/day for 2 days (days 5 and 6).

As previously reported,[12] patients in complete remission in the 9803 trial were randomized between an outpatient regimen of six monthly courses of daunorubicin 45 mg/m^2 intravenously or idarubicin 9 mg/m^2 intravenously on day 1 with subcutaneous cytarabine arabinoside 60 mg/m^2/12 h for 5 days (days 1 to 5) without G-CSF prophylaxis, or an intensive in-patient regimen with a single post-remission course identical to the first induction course including G-CSF prophylaxis. There was no maintenance therapy in this trial. As more recently reported,[13] patients in complete remission in the 9801 trial received a more intensive in-patient regimen based on two courses of intermediate-dose cytarabine arabinoside: cytarabine arabinoside 1000 mg/m^2/12 h by intravenous IV bolus for 4 days with daunorubicin 80 mg/m^2 or idarubicin 12 mg/m^2 (according to first randomization), given on day 1 for the first course and on days 1-2 for the second course. Patients in continuous complete remission after these two consolidation courses were randomized between a maintenance regimen with recombinant interleukin-2 (aldesleukin) 5×10^6 units/m^2/day subcutaneously 5 days/month, for 12 months, or no further treatment.

Decision index

The decision index was defined according to Malfuson *et al.*[5] As the age criterion of 75 years old or more taken into consideration by this decision index was not relevant to the present cohort, only performance status and white blood cell count criteria were used to define patients with an unfavorable index. Briefly, an unfavorable index was assigned to patients with high-risk cytogenetics and/or the two following factors: a performance status score of 2 or more and a white blood cell count of 50×10^9/L or more. In the absence of these criteria, patients were considered to have a favorable index.

Response criteria

Responses were classified according to International Working Group criteria.[14] Induction death was defined as death occurring before response evaluation unless evidence of resistant disease (defined according to International Working Group criteria[14]) was provided at least 7 days after conclusion of the chemotherapy.

Cytogenetics

Cytogenetic abnormalities were evaluated according to ISCN criteria;[15] with at least 15 normal mitoses to define cytogenetically normal AML; t(8;21), inv(16) and t(16;16) were considered to be favorable risk findings. According to the ALFA cytogenetic classification, the unfavorable-risk subset included patients with del(5q)/-5, del(7q)/-7, 11q23 anomaly [except for t(9;11)], t(6;9), complex karyotype (≥ 3 abnormalities), or 3q26 abnormalities. All other aberrations as well as normal karyotypes were included in the intermediate-risk subset.

Endpoints and statistical methods

The primary endpoints were overall survival and overall survival from complete remission, using the first day of induction therapy or date of complete remission as the landmark, respectively. Patients were censored at the date of last contact if alive. Survival life-tables were estimated with the Kaplan-Meier method,[16] with median follow-up determined according to Korn *et al.*[17] Secondary endpoints were disease-free survival measured from complete remission date considering death and relapse as events, and post-remission treatment-related mortality, measured as the cumulative incidence of death in first complete remission within 1 year of treatment onset, considering relapse as a competing risk. All analyses were stratified on front-line anthracycline randomization, regrouping the two 9801 idarubicin arms to form only two groups in total (daunorubicin and idarubicin). For this purpose, bivariate logistic regression was used for dichotomous variables, and stratified log-rank tests for survival analysis. All tests were two-sided with an alpha value of 0.05. All analyses were carried out using Statview (SAS, Cary, NC, USA) and R 2.10.1 software.

Results

Patients' characteristics

A total of 211 patients with *de novo* AML and aged 65 to 70 were identified as the overlap population: 76 patients from the ALFA-9801 trial and 135 from the ALFA-9803 trial (Figure 1). Their median age was 68 years. Fifty-one patients (24%) had a performance status of 2 or higher. The median white blood cell count was 6.0×10^9/L (range, 0.1×10^9/L to 270×10^9/L). Cytogenetic risk was favorable in 9 patients (4%), intermediate in 118 (56%, including 88 with cytogenetically normal AML, 42%), unfavorable in 54 (26%), and not available in the remaining 30 (14%) patients. The ALFA decision index[5] was favorable in 113 patients, unfavorable in 66 patients, and not evaluable in the remaining 32 patients. As expected, patients enrolled in the 9801 trial were younger than those enrolled in the 9803 trial (median, 67 *versus* 68 years; $P<0.001$), but white blood cell count (median, 7.4×10^9/L *versus* 5.5×10^9/L; $P=0.30$) and cytogenetics (unfavorable cytogenetics in 24% *versus* 27%; $P=0.49$) were similar in the two trial subgroups (Table 1).

Response to induction therapy

Overall, 130 patients (62%) achieved a complete remission, including 8, 80, 24 and 18 patients, with favorable, intermediate, unfavorable and missing cytogenetics, respectively. One hundred and twenty-three of those patients reached complete remission after one cycle of treatment. Fourteen (50%) and 21 (35%) of the 28 and 60 patients resistant to the first induction cycle in the 9801 and 9803 trials, respectively, received salvage therapy. Respectively, five and two of those patients achieved complete remission after salvage therapy. Eighty-one patients failed to reach complete remission because of death during induction (n=12; 5%) or resistant disease (n=69; 33%). There were no differences in the rates of complete remission, complete remission after one course of treatment, induction deaths or resistant disease between the two trial subgroups (Table 2).

Impact of trial on overall survival

The median follow-up of the 211 patients was 34 months. In univariate analysis, only karyotype affected overall survival [hazard ratio=1.8 (1.2-2.6) in high-risk cytogenetics versus others, $P=0.002$], but not age, white blood cell count greater than 50×10^9/L, or performance status score of 2 or more (Table 3). Similar results were obtained in a multivariable analysis (*data not shown*). The ALFA decision index was validated in this cohort with a

Table 1. Patients' characteristics.

	Total	ALFA-9801	ALFA-9803	P
Patients (N)	211	76	135	
Age (years), median	68	67	68	<.001
Gender (male/female), N	110/101	45/31	65/70	0.16
Performance status ≥ 2 (N, %)	51 (24)	15 (20)	36 (27)	0.29
WBC ($x10^9$/L), median [range]	6.0 [0.1-270]	7.4 [0.1-218]	5.5 [0.5-270]	0.30
French-American-British classification, N (%)				0.08
M0,6-7	18 (8)	12 (16)	6 (4)	
M1-2	121 (57)	41 (54)	80 (59)	
M4-5	59 (28)	19 (25)	40 (30)	
Not available	13 (7)	4 (5)	9 (7)	
Cytogenetic risk, N (%)				0.49
Favorable	9 (4)	3 (4)	6 (4)	
Intermediate	118 (56)	50 (66)	68 (50)	
Unfavorable	54 (26)	18 (24)	36 (27)	
Not available	30 (14)	5 (6)	25 (19)	
Decision index, N (%)				0.92
Favorable	113 (54)	42 (55)	71 (53)	
Unfavorable	66 (31)	25 (33)	41 (30)	
Not available	32 (15)	9 (12)	23 (17)	

WBC: white blood cell count.

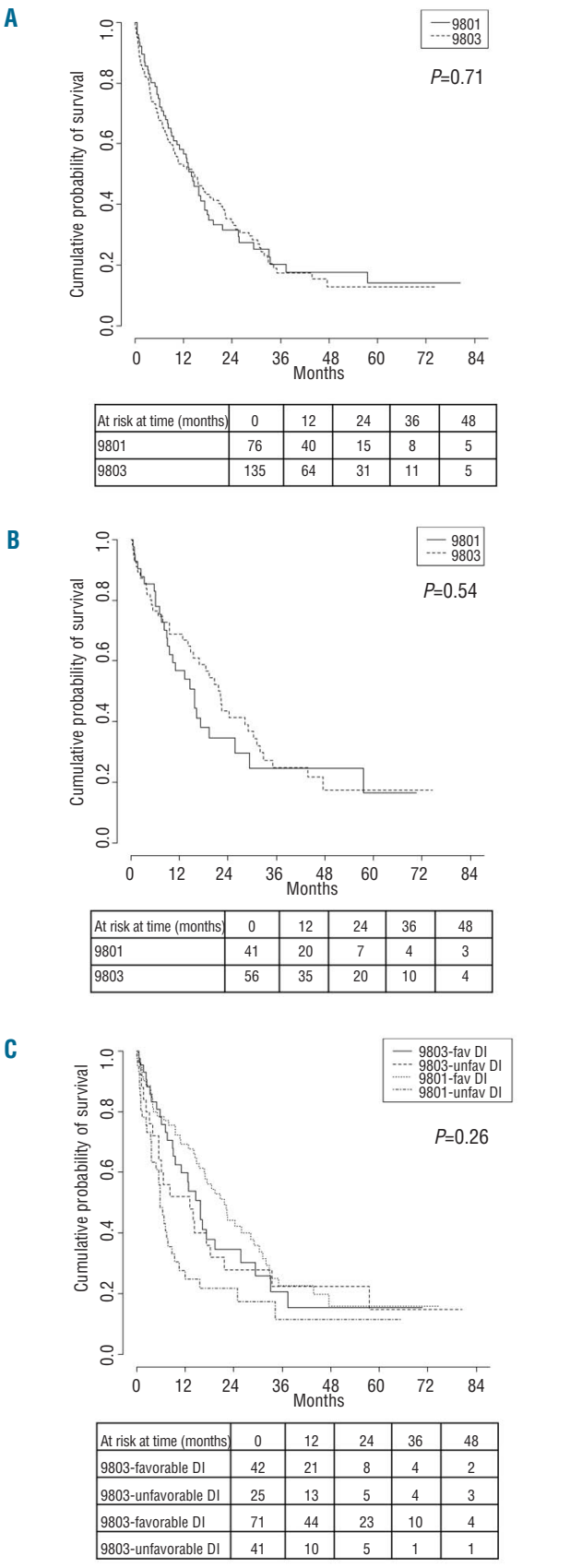
Table 2. Response to induction therapy.

	Total	ALFA-9801	ALFA-9803	P
Patients (N)	211	76	135	
Complete remission	130 (62%)	53 (70%)	77 (57%)	0.17
Complete remission after one course	123 (58%)	48 (63%)	75 (56%)	0.46
Induction death	12 (5%)	3 (4%)	9 (7%)	0.55
Resistant disease	69 (33%)	20 (26%)	47 (36%)	0.22

Table 3. Prognostic factors for overall survival and overall survival from complete remission (CR).

	Overall Survival (n=211)		Overall survival from CR (n=130)
	P	HR [95% CI]	P
Unfavorable cytogenetics	0.002	1.8 [1.2 – 2.6]	0.23
Performance score ≥ 2	0.11		0.86
WBC ≥ 50 $x10^9$/L	0.12		0.95
Age	0.24*		0.28*
Trial 9801 *versus* 9803	0.71		0.46
Unfavorable decision index	0.004	1.64 [1.17 – 2.30]	0.43

**remained non-significant even after adjusting for trial (P=0.17); HR: hazard ratio; CI: confidence interval; WBC: white blood cell count.*

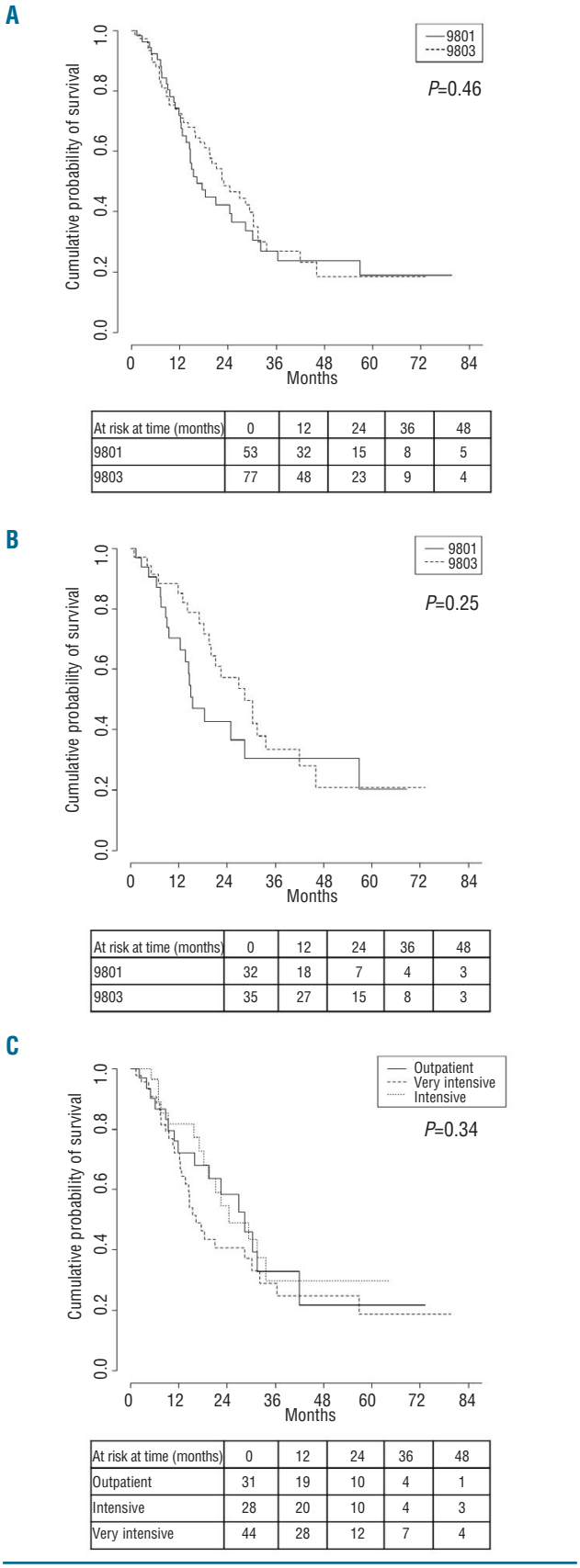


At risk at time (months)	0	12	24	36	48
9801	76	40	15	8	5
9803	135	64	31	11	5

At risk at time (months)	0	12	24	36	48
9801	41	20	7	4	3
9803	56	35	20	10	4

At risk at time (months)	0	12	24	36	48
9803-favorable DI	42	21	8	4	2
9803-unfavorable DI	25	13	5	4	3
9803-favorable DI	71	44	23	10	4
9803-unfavorable DI	41	10	5	1	1

Figure 3. Overall survival according to ALFA 9801 and 9803 trials. (A) Overlap population (n=211). (B) Patients with CBF-AML or cytogenetically normal AML (n=97). (C) Patients with a favorable (n=113) or unfavorable (n=66) decision index (DI) score.



At risk at time (months)	0	12	24	36	48
9801	53	32	15	8	5
9803	77	48	23	9	4

At risk at time (months)	0	12	24	36	48
9801	32	18	7	4	3
9803	35	27	15	8	3

At risk at time (months)	0	12	24	36	48
Outpatient	31	19	10	4	1
Intensive	28	20	10	4	3
Very intensive	44	28	12	7	4

Figure 4. Outcome after complete remission (CR) according to trial or post-remission therapy. (A) Overall survival (OS) from CR in all patients who achieved a CR (n=130). (B) OS from CR in patients with CBF-AML or cytogenetically normal AML (n=67). (C) OS from CR in patients starting planned post-remission treatment (n=103).

2-year overall survival of 41% (95% CI: 31-50%) and 23% (95% CI: 13-34%) in patients with a favorable and unfavorable decision index, respectively (P=0.004). The overall 2-year overall survival was 33% (95% CI: 26-40%). Two-year estimates were 32% (95% CI: 20-43%) in the 9801 trial (n=76) and 34% (95% CI: 26-43%) in the 9803 trial (n=135; P=0.71; Figure 3A). In the 97 patients with favorable (n=9) or normal (n=88) karyotype, the 2-year overall survival was 40% (95% CI: 29-50%), and was similar in the two trials [35% in the 9801 (95% CI: 19-51%) and 44% in the 9803 (95% CI: 32-57%), P=0.54; Figure 3B]. Analysis of the 88 patients with cytogenetically normal AML gave similar results (P=0.34). The overall survival of the 113 patients with a favorable decision index was comparable in the 9801 and 9803 trials, with 2-year overall survival rates of 35% (95% CI: 31-50%) and 44% (95% CI: 31-50%), respectively (P=0.26; Figure 3C).

Among the 130 patients who achieved a complete remission, 88 relapsed and 79 died, including seven who died in first complete remission. Five deaths in complete remission occurred during the first year of treatment, four in the 9801 trial, and one in the 9803 trial, resulting in a treatment-related mortality of 8% (95% CI: 3-21%) and 1% (95% CI: 0-9%), respectively (P=0.12). The 2-year disease-free survival of all 130 patients who achieved complete remission, regardless of post-remission therapy received, was 23% (95% CI: 14-30%), and was unaffected by trial [19% in the 9801 trial (95% CI: 7-30%) and 25% in the 9803 trial (95% CI: 14-36%), P=0.51]. The estimated 2-year overall survival from complete remission was 46% (95% CI: 37%-56%) and similar in both trials, with estimates of 42% (95% CI: 28-57%) and 49% (95% CI: 36-61%) in the 9801 and 9803 trials, respectively (P=0.46; Figure 4A). In univariate analysis, cytogenetics, age, and white blood cell count did not have a significant impact on overall survival from complete remission (Table 3).

No difference was observed when focusing on the 67 patients who achieved complete remission and who had core binding factor (CBF)-AML (n=8) or cytogenetically normal AML (n=59) [2-year overall survival from complete remission estimates, 43% in the 9801 trial (95% CI: 24-62%) and 57% in the 9803 trial (95% CI: 39-75%); P=0.25; Figure 4B]. The overall survival after complete remission of the patients with cytogenetically normal AML was also similar in the two trials (P=0.32). Only 24 patients with unfavorable karyotype reached complete remission, with similar overall survival rates from complete remission in both trials [33% at 2 years in the 9801 trial (95% CI: 2-64%) and 24% in the 9803 trial (95% CI: 1-49%), P=0.55]. Finally, in the 79 patients with a favorable decision index, there was a trend to a better overall survival from complete remission in the less intensive 9803 trial (43% at 2 years in the 9801 trial [95% CI: 24-61%] and 58% in the 9803 trial [95% CI: 42-73%], P=0.14).

Impact of post-remission strategy on overall survival

No patient received allogeneic or autologous stem cell transplantation in first complete remission. Among the 130 patients who achieved complete remission, 27 (21%) did not receive the planned post-remission therapy: 9/53 (17%) and 10/77 (13%) patients were considered ineligible for the planned post-remission or second randomization in the 9801 and 9803 trials, respectively. An additional eight (10%) patients refused the second randomization of the 9803 trial, and received the outpatient scheme. We analyzed the outcome of the remaining 103 patients who started the planned post-remission therapy, whether or not they completed the full number of courses *per* protocol: 44 in the more intensive 9801 trial, 28 in the intensive 9803 arm and 31 in the outpatient 9803 arm. Cytogenetics were favorable, intermediate, unfavorable, and missing in 7, 63, 21 and 12 cases, respectively. The estimated 2-year overall survival rates from complete remission in the three subsets (more intensive 9801 trial, intensive 9803 arm and outpatient 9803 arm) were 41% (95% CI: 28-57%), 55% (95% CI: 34-75%), and 58% (95% CI: 41-79%), respectively (Figure 4C; P=0.34). Estimated 2-year disease-free survival was also comparable in the three subsets [19% (95% CI: 7-30%), 30% (95% CI: 12-49%), and 28% (95% CI: 10-46%), respectively; P=0.37].

Discussion

There is no validated standard post-remission therapy for older AML patients once they have reached complete remission after intensive induction chemotherapy. In previous randomized trials, the outcome of patients who achieved complete remission was similar whatever the intensity of post-remission treatment.[8-10,18,19] A retrospective analysis of consecutive CALGB trials in older AML patients also failed to show a benefit for overall survival of repeated consolidation courses, including the use of cytarabine by continuous infusion or with intermittent high doses.[20] From 2000 to 2006, the ALFA ran two concomitant trials: one designed for older patients aged 65 years or more (9803 trial), and a more conventional AML strategy designed for patients aged 50-70 years (9801 trial). The 9803 trial was the first to demonstrate the superiority of an outpatient post-remission regimen over a single intensive reinduction course. The present analysis of the overlap population of patients aged 65 to 70 with *de novo* AML (most of whom had intermediate-risk cytogenetics) concomitantly enrolled in the 9801 and 9803 trials suggests that there is no apparent benefit from intensifying the post-remission treatment in patients in this age range, using either one or two intensive consolidation courses.

In this comparison, the patients and their disease characteristics were comparable in the two trial subgroups, except for a statistically significant 1-year median age difference probably of no clinical relevance in the age interval considered. The proportion of patients receiving idarubicin was higher in the 9801 trial, but, although there was a beneficial effect on complete remission rates in favor of the idarubicin arms in trial 9801,[21] anthracyclines had no effect on overall survival or disease-free survival in either of the two trials.[12,21] In addition, all analyses were stratified on the anthracycline drug used for each patient. As both trials were run concurrently in most sites, some bias may have been present, with patients with poorer status being preferentially accrued into the less intensive 9803 trial. However, patients had comparable white blood cell counts, cytogenetics and performance status in the two trials (Table 1; all P>0.20). Furthermore, such a potential bias should have favored the more intensive 9801 trial, when our results show that outcomes were strictly superimposed in the two trials.

A recent European study has showned that intensified anthracycline doses during induction may be of benefit to older AML patients, but only up to 65 years of age.[7] Although conducted in a limited number of patients, the present study failed to demonstrate any substantial benefit from intensifying the post-remission chemotherapy with two courses of intermediate-dose cytarabine arabinoside, possibly due to a higher treatment-related mortality resulting from this strategy as compared to less intensive approaches. Conversely, we did not observe a significant benefit of outpatient over intensive courses as seen in the global 9803 cohort.[12] This may be due to the smaller number of patients analyzed here, or to the selection of patients with overall better-risk cytogenetics due to exclusion of cases of secondary AML. Younger patients with *nucleophosmin1* (*NPM1*)-mutated AML without *fms-like tyrosine kinase 3* (*FLT3*) internal tandem duplication (*FLT3*-ITD), who often have a normal karyotype,[22] share a favorable prognosis with patients with CBF-AML after chemotherapy alone.[23] *NPM1* mutations also have a favorable prognostic impact in older AML patients.[24] Molecular data were not available in our cohorts of patients. However, the relatively small number of patients with CBF-AML or cytogenetically normal AML as a whole did not seem to benefit from the intensification of post-remission treatments, the CBF-AML subgroup being too small to be individualized in this study. Restricting our analyses to cytogenetically normal AML only did not affect these conclusions.

Even though restricted to patients under 70 years, most of whom had intermediate-risk cytogenetics, our study population included patients not likely to benefit from intensive therapy according to the decision index our group has proposed,[5] and should instead be candidates for investigational therapies. Restricting our analysis to patients with a favorable decision index, mainly by excluding patients with high-risk cytogenetics, there was still no benefit from a more intensive strategy in terms of either global strategy or of post-remission therapy, as assessed by overall survival and overall survival from complete remission, respectively.

Apart from the overall lower dose intensity in the 9803 trial than in the 9801 trial, a number of differences between the two trials may have affected patients' outcome. G-CSF, used only during the induction and reinduction courses of the 9803 trial, was shown to improve complete remission rates in some studies.[25] A second difference between the three post-remission schemes was the higher cumulative dose of anthracycline delivered in the less intensive 9803 outpatient arm (Figure 2). It may be that increasing the cumulative dose of anthracycline prolongs remission duration, as suggested by the increased remission rate observed in older AML patients given a doubled dose of daunorubicin during induction.[7] Conversely, it is unlikely that the interleukin-2 maintenance of trial 9801 could have affected outcome, as only 17 patients were randomized to receive maintenance, and interleukin-2 was not found to affect survival in several studies, including our 9801 trial.[13,26]

Overall, our findings suggest that in older patients with AML in complete remission, there is no apparent benefit from using an intensified post-remission treatment scheme derived from younger adult AML protocols. Whether this may also hold true in the selected subgroups of patients with normal karyotype and favorable genotypes or with favorable karyotype remains to be determined. In a large retrospective analysis of older patients with CBF-AML, use of intermediate-dose cytarabine, compared to less intensive consolidation therapies, appeared to be of possible benefit with regards to survival, at least in those carrying an *AML1/ETO* fusion gene.[27] Finally, the overall disappointing results of current intensive strategies in older AML patients should prompt investigation of alternative post-remission treatments in the majority of these patients, using novel agents and/or novel allogeneic stem cell transplantation procedures, rather than modulating the dose intensity of conventional chemotherapy.

Authorship and Disclosures

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