Risk factors and decision criteria for intensive chemotherapy in older patients with acute myeloid leukemia

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ABSTRACT

Background
There is a need for standardization of treatment decisions in older patients with acute myeloid leukemia. The aim of the present study was to analyze the decisional value of poor risk factors in 416 elderly patients treated in the ALFA-9803 trial in order to derive a decisional index.

Design and Methods
Standard multivariate analysis was used to identify risk factors for overall survival. Risk factors were then considered as good decision tools if associated with a frequency >10% and a false positive rate <10% in predicting overall survival as poor as observed after low-dose cytarabine therapy (25% survival or less at 12 months).

Results
Among six independent risk factors (age, performance status, white blood cell count, hematopoietic cell transplantation comorbidity index, infection at baseline, and cytogenetics), cytogenetics was the only potent, independent decision tool. High hematopoietic cell transplantation comorbidity index scores or infections were found too rarely to guide further decisions. The three other factors (age, performance status, and white cell count) needed to be combined to provide a good specificity. The proposed decisional index, therefore, included high-risk cytogenetics and/or the presence of at least two of the following criteria: age ≥75 years, performance status ≥2, and white cell count $\geq 50\times10^9$/L. This simple two-class decisional index, which was validated in an independent patient set, enabled us to discriminate 100 patients (24%) who had an estimated overall survival of only 19% at 12 months, with a good 9% false positive rate.

Conclusions
We propose waiting for cytogenetic information before making treatment decisions in elderly patients with acute myeloid leukemia. Those patients with unfavorable cytogenetics, as well as patients with at least two of the following features, age ≥75 years, performance status ≥2, and white cell count $\geq 50\times10^9$/L, should not be considered for standard intensive chemotherapy (ClinicalTrials.gov identifier: NCT00363025).

Key words: elderly, acute myeloid leukemia, prognosis, risk factors, decision criteria.

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Introduction

Acute myeloid leukemia (AML) is predominantly a disease of the elderly as more than half of the patients with this malignancy are over 60 years old. In older patients, the benefit associated with standard intensive chemotherapy remains debated because of excessive toxicity and short duration of response. Factors related to age, including poor performance status (PS), pharmacodynamic changes, and organ dysfunctions, may negatively affect treatment tolerance.[1-5] Factors related to disease biology, including more frequent prior myelodysplastic syndrome (MDS), expression of a multidrug resistance phenotype, and unfavorable karyotype, may lower the response rate and response duration.[1-5]

It is becoming critical to define older patients who are not eligible for intensive chemotherapy, as many of the new agents developed in AML are merely proposed to those patients.[6] In some recent studies testing less intensive approaches, the definition of non-eligible patients was simply based on the presence of at least one of the following characteristics: age of 70 years or more, PS of 2 or more, post-MDS AML, or unfavorable cytogenetics. There are, however, no standardized criteria for this selection process. Some published studies propose using weighted prognostic scores based on poor risk factors identified by multivariate analysis.[7] Other reports focus on the impact of associated comorbidities. For instance, a refined Hematopoetic Cell Transplantation Comorbidity Index (HCTCI) was recently developed in patients who were candidates for allogeneic stem cell transplantation,[8] and then successfully tested in older patients with AML.[9,10] However, poor risk factors could be suboptimal decision tools at the level of individual patients. Indeed, a very potent risk factor in terms of hazard ratio (HR) and p value may be a poor discriminating factor if associated with a low specificity and high false positive rate (FPR). In addition, any potential decision criterion should be relatively frequent in the population of patients in order to be considered clinically useful.

The primary objective of this study was to determine how poor risk factors may be used as decision criteria in older patients intensively treated for AML. The study was performed in the population of 416 patients prospectively treated in the multicenter Acute Leukemia French Association (ALFA) 9803 trial.[11] We first identified independent prognostic factors, including comorbidities, in this series of patients. We then tested these factors or combinations of factors for their decisional characteristics including prevalence and FPR in order to propose a decisional index. The end-point was overall survival.

In order to define whether intensive chemotherapy would be futile, we used the results associated with low-dose cytarabine in patients considered as unsuitable for intensive chemotherapy as a comparator. In these poor-risk patients, overall survival rates have been reported as approximately 50% at 4 months and 25% at 12 months.[12]

Design and Methods

Study population

The study population comprised the 416 patients treated in the ALFA-9803 trial.[11] This study was approved in June 1999 by the institutional review board (IRB) of Hôpital Pitié-Salpêtrière, Paris, France, and conducted in accordance with the Declaration of Helsinki. Eligible patients were those aged 65 years or more with newly-diagnosed previously untreated AML with 20% or more myeloid marrow blasts (promyelocytic leukemia excluded), either *de novo* or evolving from a prior MDS, in the absence of: (i) central nervous system involvement; (ii) prior exposure to chemotherapeutic agents and/or radiotherapy; (iii) prior congestive heart failure requiring treatment and/or left ventricular systolic ejection fraction below the normal range; (iv) a creatinine or bilirubin level > 2 times the upper limit of normal, except if AML-related and (v) PS>3; and (vi) uncontrolled severe infection. All patients gave their signed informed consent to participation in the study.

Treatments

Patients were randomized at baseline (R1 randomization) to receive either daunorubicin or idarubicin as an anthracycline for the whole treatment period. Induction chemotherapy consisted of a 4+7 course with either daunorubicin at a daily dosage of 45 mg/m^2 or idarubicin at a daily dosage of 9 mg/m^2 for 4 days (days 1 to 4) in combination with 200 mg/m^2 cytarabine per day as a continuous intravenous infusion for 7 days (days 1 to 7). Lenograstim granulocyte colony-stimulating factor was administered to all patients from day 9 until myeloid recovery for a maximum of 28 days. A salvage course could be offered to patients with persistent leukemia. Salvage therapy consisted of six 1-hour intravenous boluses of intermediate-dose cytarabine (500 mg/m^2/12h, days 1 to 3) combined with mitoxantrone at a daily dosage of 12 mg/m^2 for 2 days (days 3 and 4), again followed by lenograstim administration. In the absence of acquired contra-indications to further intensive chemotherapy, patients in complete remission were eligible for a second randomization (R2) between ambulatory and intensive post-remission therapy. Ambulatory consolidation consisted of six monthly courses with either 45 mg/m^2 daunorubicin or 9 mg/m^2 idarubicin for 1 day (day 1) in combination with 60 mg/m^2/12h cytarabine as home subcutaneous infusions for 5 days (days 1 to 5). Intensive consolidation was an exact repetition of the first induction course and administered to hospitalized patients.

Methods

The first part of the study was a standard multivariate identification of bad-prognosis factors for overall survival in this population of patients. The following covariates were included in the model: (i) age; (ii) PS (0-1 *vs.* 2-3); (iii) cytogenetics (high- *vs.* standard-risk); (iv) white blood cell count (WBC); (v) post-MDS AML; and (vi) HCTCI and all HCTCI items (Table 1). High-risk cytogenetics features were defined as monosomy 7,

Table 1. Hematopoietic cell transplantation co-morbidity index.

Item	Definition	HCTCI score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmia	1
Cardiac other[a]	Myocardial infarction or coronary artery disease	1
	Heart valve disease, except mitral valve prolapse	3
Cerebrovascular	Transient ischemic attack, cerebrovascular accident	1
Diabetes	Requiring insulin or oral hypoglycemics	1
Peptic ulcer	Requiring treatment	2
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Moderate pulmonary[a]	Dyspnea on slight activity or DLCO and/or FEV_1 66-80%	2
Moderate/severe renal	Serum creatinine >176.8 mM/L, on dialysis, or prior renal transplantation	2
Mild hepatic[a]	Chronic hepatitis, bilirubin 1.0-1.5 ULN, AST/ALT 1.0-2.5 ULN	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consultation or treatment	1
Obesity	Body mass index >35 kg/m^2	1
Infection	Requiring continuation of antimicrobial therapy after day 0	1
Prior solid tumor[b]	Treated at any past time point, excluding non-melanoma skin cancer	3

Adapted from Sorror et al.[8] [a]congestive heart failure, severe pulmonary, and moderate/severe liver disease are not mentioned, as never observed in the study population; [b]prior exposure to chemotherapeutic agents and/or radiotherapy was a non-eligibility criterion for the study population; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; CTD: connective tissue disease; DLCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in 1 second; ULN: upper limit of normal: AST: aspartase transferase; ALN: alanine transferase.

presence of abnormalities of both chromosomes 5 and 7, 3q26 abnormalities, and a complex karyotype with five or more anomalies.[11] Given the trial eligibility criteria described earlier, congestive heart failure, severe pulmonary disease, and moderate/severe liver disease were never observed in the study population. Moderate/severe renal failure (serum creatinine level >176.8 μM/L) was present in only 11 patients and always related to AML, according to the treating physician. To take into account the patient's renal function more appropriately, the creatinine-based glomerular filtration rate was estimated using the Cockroft-Gault formula and tested as well. Mild hepatic abnormalities and moderate pulmonary failure were considered only if due to a liver or respiratory disease that antedated the AML. For continuous co-variates, best cut-off values were determined for the overall survival end-point and eventually used to classify patients.

The second part of the study was to analyze all identified risk factors for their decisional characteristics. To this purpose, each risk factor was characterized by its prevalence and by its sensitivity and specificity in terms of predicting 4-month and 12-month overall survival. The sensitivity of a bad-prognosis factor corresponded to the rate of patients who did present the factor in the subset of those who died before 4 or 12 months. The specificity of a bad-prognosis factor was reflected by its FPR, which corresponded to the rate of patients who presented the factor in the subset of those who survived more than 4 or 12 months. Of note, if p represents the probability of failure for the whole population, the prevalence of a criterion (f) is related to its sensitivity (S) and FPR by the following relationship: $f = p \times S + [1 - p] \times FPR$. We arbitrarily considered a poor risk factor as a good decisional criterion if: (i) predictive of a 12-month outcome as poor as that observed in unfit patients when treated by low-dose cytarabine (12-month overall survival ≤25%); (ii) its prevalence was >10%; and (iii) it was associated with a FPR <10%, meaning that less than 10% of survivors presented this bad-prognosis factor. Factors that fulfilled these prerequisites were considered as a good decisional criteria by themselves. Other factors with a prevalence >10% were considered as not discriminatory enough to guide decision by themselves, but good candidates to be tested in combination.

Statistical considerations

Binary variable comparisons were performed using Fisher's exact test. Medians were compared using the Mann-Whitney test. Responses were defined according to recommendations of the International Working Group.[13] Induction death was defined as death occurring before response evaluation unless evidence of resistant disease was provided at least 7 days after conclusion of the chemotherapy. The median follow-up of living patients was 34 months. Mortality was estimated by the Kaplan Meier method and compared with the log-rank test.[14,15] Multivariate analyses were performed using logistic regression or Cox models and tested by the log likelihood ratio test. Best cut-offs were determined using a corrected minimum p value method based on an approximation to the improved Bonferroni's inequality.[16] Hazard ratios are given with their 95% confidence interval (CI). All calculations were performed using STATA software, version 9.0E (Stata Corporation, College Station, TX, USA).

Results

Patients' characteristics and co-morbidities

The main characteristics of the 416 patients are presented in Table 2. The median age was 72 years. Of interest, 344 patients (83%) had at least one of the following characteristics: age of 70 years or more, PS of 2 or more, post-MDS AML, or unfavorable cytogenetics. The most frequent comorbidities were coronary artery disease (42 patients; 10%), arrhythmia (33 patients; 8%), infection (32 patients; 8%), diabetes (30 patients; 7%),

moderate pulmonary disease (20 patients; 5%), a psychiatric disturbance (17 patients; 4%), and obesity (12 patients; 3%). Probably because of the first selection step based on trial eligibility criteria, a high HCTCI score of 3 or more discriminated only 21 high-risk patients (5%). Interestingly, the HCTCI score did not correlate with either PS (p=0.30) or advanced age (p=0.77). Conversely, a strong correlation was observed between PS and WBC. The median WBC was 4.4×10^9/L in patients with a PS 0-1 as compared to 13.9×10^9/L in those with a PS 2-3 (p=0.002). Of note, despite the fact that active infection was a criterion for non-eligibility, 32 patients (8%) with infection at baseline were nevertheless enrolled as investigators considered these infections as controlled at the time of enrollment. Infection was defined here as a microbiologically and/or clinically documented infection which required continuation of antimicrobial therapy after initiation of chemotherapy. A single positive blood culture, as well as positive urine or sputum cultures, were not considered in the absence of clinically documented infection. All 32 patients with infection at baseline had had pneumonia and/or septicemia.

General outcome

In this cohort of patients, the complete remission rate was 56.7% and the induction death rate was 9.6%.[11] Overall, the estimated overall survival was 77% (95% CI, 73 to 81) at 4 months and 50% (95% CI, 45 to 54) at 12 months. Table 3 shows the comparison of the ALFA-9803 treatment arms. As previously reported,[11] no significant difference in complete remission rate or overall survival was observed between the daunorubicin and idarubicin randomization arms. Conversely, among patients who achieved complete remission and who were then randomized to ambulatory *vs.* intensive post-remission therapy, overall survival from complete remission was significantly longer in the ambulatory arm.

Risk factors for overall survival

Table 4 provides the results of multivariate analysis for overall survival with hazard ratios and p values for the six identified independent risk factors. Prevalence, induction death rate, and estimated 4-month and 12-month overall survival rates are also indicated. The best cut-offs for age and WBC were 75 years and 50×10^9/L, respectively. Although present in only 5% of patients, a HCTCI score ≥3 was independently predictive of worse overall survival (Figure 1 and Table 4). Among all HCTCI items present in more than 5% patients (coronary artery disease, arrhythmia, infection, and diabetes), only infection at baseline had a significant impact on overall survival and this independently of the HCTCI value. In this series of patients, neither serum creatinine level nor glomerular filtration rate had a significant impact on overall survival, even in univariate analysis. Of note, post-MDS AML which was diagnosed in 63 patients (15%), was not predictive of a shorter overall survival, even in univariate analysis. We have already reported that the cumulative incidence of relapse was higher in patients with post-MDS AML but due to more frequent relapses as MDS rather than AML and a longer post-relapse survival, this did not translate

Table 2. Characteristics of the study population.

Patients (n)	416
Sex ratio (male/female)	225/191
Age	
Median age (range)	72 years (65-85)
Age ≥75 years (n)	84
Age ≥80 years (n)	9
Performance status (n)	
0	109
1	193
2	102
3	12
HCTCI score (n)	
0	268
1	85
2	42
3+	21
WBC	
Median (range)	5.3×10^9/L (0.1-420)
AML type (n)	
de novo acute myeloid leukemia	353
post-MDS acute myeloid leukemia	63
Cytogenetics (n)	
Not done	27
Failure	50
High-risk[a]	49
Standard-risk	290

[a]*High-risk cytogenetics was defined here as monosomy 7, presence of abnormalities of both chromosomes 5 and 7, 3q26 abnormalities, and complex karyotype with five or more anomalies.*[11]

Table 3. Comparison of the ALFA-9803 treatment arms.

First randomization	*Daunorubicin arm*	*Idarubicin arm*	*p value*
Patients (N.)	209	207	–
Age ≥75 years	46	38	0.39
Performance status ≥2	51	63	0.19
Infection	15	17	0.72
HCTCI ≥3	10	11	0.83
WBC ≥50×10^9/L	36	30	0.50
High-risk cytogenetics[a]	25	24	0.99
Complete response rate[b]	54%	59%	0.28
2-year overall survival[b]	27%	28%	0.37
Second randomization	*Ambulatory arm*	*Intensive arm*	*p value*
Patients (N.)	82	82	–
Age ≥75 years	13	9	0.49
Performance status ≥2	17	18	0.99
Infection	1	4	0.37
HCTCI ≥3	1	3	0.62
WBC ≥50×10^9/L	14	10	0.51
High-risk cytogenetics[a]	5	3	0.49
2-year overall survival from complete remission[b]	56%	37%	0.03

[a]*High-risk cytogenetics was defined here as monosomy 7, presence of abnormalities of both chromosomes 5 and 7, 3q26 abnormalities, and complex karyotype with five or more anomalies;*[11] [b]*detailed in reference 11.*

into a shorter overall survival.[11]

Among these six identified risk factors, three were associated with the predefined target in terms of predicting poor overall survival (4-month overall survival ≥50% and 12-month overall survival ≤25%), namely high-risk cytogenetics, HCTCI ≥3, and infection at baseline. However, two of these factors did not reach the 10% prevalence level (HCTCI and infection). The remaining three factors (age ≥75 years, PS ≥2, WBC ≥50×10^9/L) did not, by themselves, reach the predefined target in terms of predicting poor overall survival since they were associated with a 4-month overall survival >50% and a 12-month overall survival >25%.

Determination of decisional criteria

Table 5 shows the sensitivity and FPR for the 4-month and 12-month overall survival end-points for the four risk factors with a prevalence >10%. The first observation is the low sensitivity of all factors for both time points. Probably because of the poor outcome of older patients with AML in general, these sensitivities were, in all cases, always less than 50%, meaning that more than half of the patients who actually died did not have the risk factor. Only high-risk cytogenetics reached the target in terms of specificity (FPR <10%). This factor could, therefore, be considered as a good decisional criterion to advise against intensive chemotherapy by itself, since it discriminated 12% of patients who had an estimated overall survival of only 9% at 12 months (95% CI, 3-20) while it was detected in only 2% of the survivors.

The other three risk factors (age ≥75 years, PS ≥2, WBC ≥50×10^9/L) lacked specificity to have an optimal decisional value by themselves. They, therefore, needed to be combined. The easiest manner to combine these factors was to define a score in which the presence of each of these factors was attributed 1 point. In the whole population, 51 patients had a score of 2 and six additional patients had a score of 3. These 57 patients (14% of the whole population) had an estimated overall survival of only 25% at 12 months (95% CI, 11-36) with a FPR of 7%.

We, therefore, tested a simple decisional index in which the presence of high-risk cytogenetics was taken into account (1 point) as well as the presence of at least two of the following factors (1 point if at least two factors): age ≥75 years, PS ≥2, WBC ≥50×10^9/L. Overall, 316 patients had a decisional index equal to 0, while 100 patients (24% of the whole population) had a decisional index >0. Based on how these decisional criteria were determined, these 100 patients should be considered as not being candidates for intensive chemotherapy. Actually, they had an estimated overall survival of only 19% at 12 months (95% CI, 12-28) with a FPR of only 9%. This estimated 19% overall survival at 12 months was significantly lower than the 50% overall survival (95% CI, 45 to 54) of the entire population of patients (p<0.001 by the log-rank test) as well as the 58% overall survival (95% CI, 52-63) of the 316 remaining patients (p<0.001 by the log-rank test) (Figure 2).

The two-class decisional index was then tested in an independent validation set of 143 AML patients with a median age of 73 years (range, 70 to 85 years) intensively treated between 1995 and 2006 in one independent French institution, with an overall median overall survival of 9 months (median follow-up, 46 months). Again, HCTCI ≥3 was observed in only 3% of these patients. High-risk cytogenetic features were found in 19 patients (14%). Age ≥75 years, PS ≥2, and a WBC>50×10^9/L were recorded for 36%, 34%, 25% patients, respectively. With respect to the 12-month overall survival end-point, FPR were 8%, 33%, 35% and

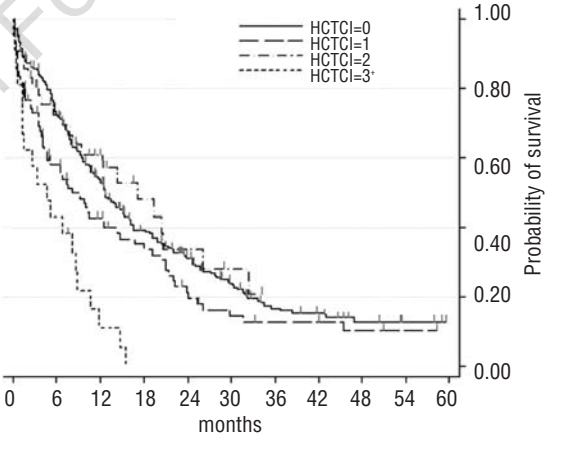

Figure 1. **Overall survival according to HCTCI score. HCTCI had a significant impact on overall survival (p<0.001 by the log-rank test), but only due to the poor outcome of the 5% patients with a HCTCI ≥3 (n=21).**

Table 4. **Bad-prognosis factors for overall survival (multivariate analysis).**

	Prevalence	*Induction death rate*	*4-month overall survival (95% CI)*	*12-month overall survival (95% CI)*	*HR (95% CI)*	*p value*
Age ≥75 years	84 (20%)	20%	68% (56-77)	40% (29-50)	1.45 (1.1-1.9)	0.01
PS ≥2	114 (27%)	18.5%	61% (51-70)	38% (28-47)	1.35 (1.0-1.8)	0.03
Infection	32 (8%)	25%	50% (32-67)	25% (11-42)	1.91 (1.2-2.9)	0.003
HCTCI ≥3	21 (5%)	24%	50% (30-71)	11% (2-29)	1.53 (1.2-1.95)	<0.001
WBC ≥50×10^9/L	66 (16%)	15%	70% (57-79)	32% (21-44)	1.69 (1.2-2.3)	0.001
High-risk cytogenetics[a]	49 (12%)	14%	49% (33-61)	9% (3-20)	3.31 (2.4-4.6)	<0.001

[a]*high-risk cytogenetics was defined here as monosomy 7, presence of abnormalities of both chromosomes 5 and 7, 3q26 abnormalities, and complex karyotype with five or more anomalies.*[11]

11% for the cytogenetic, age, PS, and WBC risk factors, respectively. In this validation set, a decisional index >0 discriminated 51 high-risk patients (36%) with an estimated overall survival of only 15% at 12 months (95% CI, 7-26) with a good FPR of 10%. Again, this estimated 15% overall survival at 12 months was significantly lower than the 43% overall survival (95% CI, 34-51) of the entire population of patients (p<0.001 by the log-rank test) or the 62% overall survival (95% CI, 51-71) of the 92 remaining patients (p<0.001 by the log-rank test).

We then attempted to compare this decisional index with a more standard prognostic score based on regression coefficients. Using the ALFA-9803 dataset, the resulting prognostic index (PI) was:

[1.264 x unfavorable cytogenetics] + [0.192 x PS] + [0.042 x age] + [0.003 x WBC].

The best statistical cut-off of the prognostic index was 4.0, corresponding to a smaller subset of 57 high-risk patients (14%). Among the 100 patients with a prognostic index of 3.61 or more, 11 patients had a decisional index equal to 0. In this 100-patient subset, the probability of death at 12 months was 78% and the FPR was 11%.

Discussion

The aim of the present study was to determine which factors associated with a poor outcome after intensive chemotherapy might be used as decisional criteria in elderly persons with AML. The goal was not to develop a statistical prediction model, as such models have been proposed by other groups.[7] The aim was to analyze each risk factor for its decisional relevance in individual patients. That was the reason why we required minimum levels for prevalence (10%), predictive value (25% OS at 12 months), and specificity (90%) to retain a risk factor as a good decisional element. As these levels were arbitrarily chosen, they might obviously be a matter of debate. It seemed to us that the results of low-dose cytarabine therapy reported in elderly persons with AML considered unsuitable for intensive treatment could serve as a good comparator to define the futility of this intensive approach in patients considered as suitable. Since we focused on the general outcome rather than on the short-term tolerance of the induction course, we retained mid-term end-points (4-month and 12-month overall survival) for this comparison. The results should have been the same if other time end-points, such as 3-month or 6-month overall survival, had been used.

An apparently trivial but important point is that patients enrolled in intensive chemotherapy trials should first be considered as eligible for intensive treatment on the basis of usual eligibility criteria and, probably, more subjectively, thus leading to an important selection step.[17] This could explain why very few patients in our study had relatively severe comorbidities or high HCTCI score. That could also explain why age did not correlate with PS and HCTCI and was not identified as a good decisional element by itself. Nevertheless, age, like PS and WBC, is a potent prognostic factor with best statistical cut-offs at 75 years in the present study and 70.4 years in a recent study by the German-Austrian AML Study Group.[4] We, however, felt that these three potent risk factors were not fully appropriate for guiding treatment decisions by themselves, as they were not able to discriminate well between patients who were not candidates *vs.* those who were candidates for intensive treatment. We thus concluded that the factors have to be combined. One manner to combine these factors could have been to derive a score based on regression coefficients from the Cox regression, as has already been proposed.[7] It seemed to us, however, that the easiest manner was to simply hypothesize and test that the presence of two of

Table 5. Decisional characteristics of poor risk factors.

	Sensitivity (%)	*FPR (%)*
For 4-month overall survival		
Age ≥75 years	28	18
PS ≥2	46	21
WBC ≥50×10⁹/L	21	15
High-risk cytogenetics[a]	26	8
For 12-month OS		
Age ≥75 years	24	15
PS ≥2	33.5	19
WBC ≥50×10⁹/L	21.5	10
High-risk cytogenetics[a]	22	2

The sensitivity corresponds to the rate of patients who did present the factor in the subset of those who died before 4 or 12 months. The false positive rate (FPR) corresponds to the rate of patients who presented the factor in the subset of those who survived more than 4 or 12 months; [a]high-risk cytogenetics was defined here as monosomy 7, presence of abnormalities of both chromosomes 5 and 7, 3q26 abnormalities, and complex karyotype with five or more anomalies.[11]

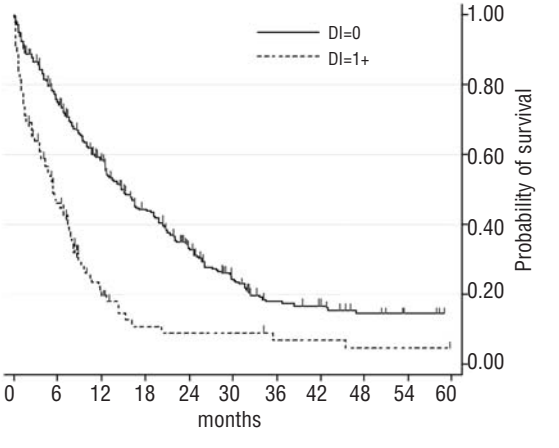

Figure 2. Overall survival according to the decisional index (DI). In the DI, the presence of high-risk cytogenetics is attributed 1 point, while the presence of at least two of the three other risk factors (age ≥75 years, PS ≥2, WBC ≥50x10⁹/L) is also attributed 1 point. The DI was equal to 0 in 316 patients and >0 in 100 patients. The estimated overall survival was 19% (95% CI, 12-28) at 12 months in the latter subgroup as compared to 58% (95% CI, 52-63) in the former subgroup (p<0.001 by the log-rank test).

these three factors could be a good decisional tool allowing better discrimination. We have shown and verified in an independent patient set that this approach is valid, allowing us to derive a very simple and practical index to guide treatment decisions.

Cytogenetics plays a very important role in this index since we conclude that it can be used alone to advise *pro* or *contra* intensive therapy. This means that the results of cytogenetic analyses must be available before treatment initiation. A recent study seems to demonstrate that this is feasible in older patients, without a deleterious impact on treatment outcome, unlike in younger patients.[18] The definition of the high-risk cytogenetic subset used in this study could be another matter of debate. The number of studies testing the prognostic impact of cytogenetics is more limited in elderly than in younger AML patients. The few classifications proposed are not concordant.[4,5,19-21] In the ALFA-9803 study, monosomy 7, presence of abnormalities of both chromosomes 5 and 7, 3q26 abnormalities, and complex karyotype with five or more anomalies were identified as associated with a worse outcome.[22] These anomalies also correspond to the core of the high-risk cytogenetic subset in studies of younger AML patients.[23] One may argue that cytogenetics is also a bad-risk factor in patients treated with low-dose cytarabine and that virtually no patients with high-risk cytogenetics will respond to this non-intensive approach, still raising the issue of the superiority of intensive chemotherapy in this very high-risk subset. We nevertheless believe that a 25% overall survival at 12 months is definitely too poor to not test alternative approaches. Some hope is being raised by new options, such as hypomethylating agents, clofarabine, or cloretazine, which have recently been associated with relatively good response rates in older patients with cytogenetically unfavorable AML or high-risk MDS.[24-28] Unfortunately, cases of good-risk cytogenetics are rare among older AML patients. In this ALFA-9803 study, only 12 patients (3%) had either t(8;21) or inv(16) and, even though their estimated 2-year overall survival was 46% compared to the 31% in patients with a normal karyotype, the difference was not statistically significant (p=0.20). Two of these 12 patients were classified as being at high risk based on the combined age/PS/WBC criteria and both died within the first 6 months. Although the presence of such favorable karyotypes is considered by many investigators as in favor of a standard intensive treatment approach, the paucity of available data does not allow specific recommendations to be made for this older population of patients.

In conclusion, we propose a two-class index as a tool to guide the decision concerning standard intensive chemotherapy in individual older patients with AML. Patients meeting usual eligibility criteria with a decisional index equal to 0 may receive intensive chemotherapy. Other patients, with a decisional index >0, because of high-risk cytogenetics and/or at least two of the three age/PS/WBC risk factors (age ≥75 years, PS ≥2, WBC ≥50×10^9/L) should be offered alternative therapies. Even if the criteria retained are not surprising, we show that this simple index is associated with good predictive and discriminating values. One may expect an approximately 60% overall survival at 12 months after intensive chemotherapy in the subset of patients considered as good candidates on the basis this index. To our knowledge, no other investigational approach currently yields comparable results.

Appendix

The following ALFA investigators participated in the study: F. Treilhou, D. Rea, A. de Labarthe, MT. Daniel, O. Maarek, E. Raffoux, N. Boissel , J. Delaunay, H. Dombret (Hôpital Saint-Louis, Paris); H. Djeda, N. Cambier, S. Darre, S. de Botton, F. Lai, B. Quesnel (CHU, Lille); JO. Bay (CHU, Clermont-Ferrand) ; MP. Chaury, C. Tisseuil, L. Remenieras, N. Gachard, P. Turlure, D. Bordessoule (CHU, Limoges); S. Rigaudeau, E. Henry, C. Terre, AL. Taksin, F. Suzan, D. Legrand, P. Rousselot, S. Castaigne (Hôpital Mignot, Versailles); J. Beaune, C. Pautas, C. Perot, K. Yakouben, S. Maury, M. Kuentz, C. Cordonnier (Hôpital Henri Mondor, Creteil); I. Dervite, P. Morel, B. Dupriez (Hôpital Schnaffer, Lens); N. Itzhar, JM. Ventelon, A. Bernheim, P. Arnaud, JH. Bourhis (Institut Gustave Roussy, Villejuif); I. Plantier, L. Detourmignies (Hôpital Provo, Roubaix); I. Garnier, JV. Malfuson, F. Desangles, T. Fagot, B. Souleau, G. Nedellec, T. de Revel (Hôpital Percy, Clamart); V. Tallon, F. Jardin, A. Stamatoulas, N. Contentin, S. Lepretre, P. Lenain, C. Bastard, H. Tilly (Centre Henri Becquerel, Rouen); B. Beve, C. Gardin, V. Eclache, JJ. Kiladjian, L. Ades, MP. Lemonnier, P. Casassus, P. Fenaux (Hôpital Beaujon, Clichy, and Hôpital Avicenne, Bobigny); K. Triana, N. Dhedin, S. Nguyen, F. Nguyen Khac, L. Sutton, S. Choquet, V. Leblond, JP. Vernant (Hôpital Pitie-Salpetriere, Paris); F. Isnard, J. Van den Akker, L. Garderet , P. Coppo, L. Fouillard, JP. Laporte, NC. Gorin, A. Najman (Hôpital Saint-Antoine, Paris); S. Glaisner, M. Janvier, A. Bourguignat, E. Baumelou, F. Turpin (Centre Rene Huguenin, Saint-Cloud, and Hôpital Foch, Suresnes); E. Lepesant, M. Macro, G. Plessis, S. Cheze, O. Reman, M. Leporrier (CHU, Caen); J. Frayfer, C. Soussain, C. Allard (Centre Hospitalier, Meaux); B. Corront, J. Provencal, C. Martin (Centre Hospitalier, Annecy); M. Blanc, J. Lespinasse (Centre Hospitalier, Chambery); M. Elhamri, A. Thiebaut, I. Tigaud, F. Nicolini, K. Bilger, A. Belhabri, J. Troncy, X. Thomas, M. Michallet (Hôpital Edouard Herriot, Lyon); E. Ferrant, O. Casasnovas, F. Mugneret, JN. Bastie, D. Caillot (CHU, Dijon), France.

Authorship and Disclosures

All authors participated actively in the study conception and design and acquisition of data. All cytogenetic data were centrally reviewed by CT. The statistical analysis was undertaken by HD. The manuscript was written by HD and CG and approved by all authors. The list of participating centers and investigators is given in the Appendix. The authors reported no potential conflicts of interest.

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