Long-term survival can be achieved in a significant fraction of older patients with core-binding factor acute myeloid leukemia treated with intensive chemotherapy

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Abstract

Acute myeloid leukemia (AML) is mainly a disease of the elderly: however, knowledge about the outcomes of treatment of core-binding factor (CBF) AML in an older population is limited. We retrospectively collected data on 229 patients with CBF-AML followed long-term in the last two decades. The 5-year overall survival was 44.2% (95% confidence interval [95% CI]: 39.9-47.5) and the 5-year event-free survival was 32.9% (95% CI: 25.5-40.1). In a subgroup of patients ≥70 years old who completed intensive therapy (induction + ≥3 courses of consolidation including autologous stem cell transplantation: 10 patients) the median event-free survival was 11.8 months (95% CI: 9.4-15.2) and overall survival was 40.0% (95% CI: 36.4-44.1) at 5 years. In univariate analysis, age ≥70 years (hazard ratio [HR]=1.78, 95% CI: 1.15-2.54, *P*=0.008), failure to achieve remission following induction (HR=8.96, 95% CI: 5.5-13.8; *P*<0.0001), no consolidation therapy (HR=0.75, 95% CI: 0.47-1.84, *P*=0.04) and fewer than three cycles of consolidation (HR=1.48, 95% CI: 0.75-3.2; P=0.0004) predicted poorer event-free survival. Our study shows that intensive therapy, in selected older CBF-AML patients, leads to longer survival. Achieving a complete remission seems to be the most important first step and at least three cycles of consolidation, an important second one. The analysis suggests that these patients should not be excluded from studies with intensive therapies.

Introduction

Acute myeloid leukemia (AML) is mainly a disease of older patients, affecting 0.11 patients for every 100,000 inhabitants per year overall, but with peak age-adjusted incidence rates ranging from 0.25/10^5 to 0.28/10^5 in the age groups 65-74 and 75-84 years, respectively.[1-3] Even though intensive chemotherapy proves successful in many cases, most patients who enjoy long-term survival are younger. In contrast, historically, treatment outcome in the elderly has been dismal, with less than 20% of patients >65 years old surviving beyond 5 years from diagnosis.[4,5]

Older patients do poorly due to both patient- and disease-associated factors, including a higher incidence of adverse disease features as well as a higher risk of early death because of comorbidities and worse performance status at diagnosis, and higher incidences of treatment-related toxicities and infectious complications.[6-10] This historical information can discourage use of intensive treatments in older patients.[1,11] However, this might be changing with advances in the prophylaxis and treatment of infections and in supportive care, with several reports describing increasingly better results in older patients.[12,13] Better understanding and more objective assessment of patients' fitness (assessment of frailty, performance status and comorbidities) can allow the use of more intensive chemotherapy in older patients.[14]

More recently, newer drugs with less toxicity and lower risk of infections, such as targeted therapy, hypomethylating agents (HMA) alone or in combination with the Bcl-2 antagonist venetoclax and low-dose chemotherapy in combination with smoothened- and sonic hedgehog-signaling inhibitor, have further broadened the treatment choices for patients considered unfit for intensive conventional chemotherapy.[15-18]

Core-binding factor (CBF)-AML is defined by the presence of t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22), and accounts for 7-15% of AML occurring in younger patients.[19-21] CBF-AML is generally considered to have a relatively favorable prognosis, as compared to other types of AML, due to its sensitivity to chemotherapy, particularly at higher doses.[22-26] This characteristic has resulted in long-term survival in approximately 60-70% of younger patients (<60 years) with CBF-AML, even without allogeneic hematopoietic stem cell transplantation (HSCT) in first complete remission (CR).[22,23] The incidence of CBF-AML decreases with age: in fact, it accounts for less than 5% of AML cases in people aged >60 years.[27] These patients' survival is poorer as, not receiving intensive therapy, relapse is much more common among them than in younger CBF-AML patients, with relapse rates of 70-80% *versus* 40%, respectively.[19,28-32] Actual data from older patients with CBF-AML are rare and consequently these patients are underrepresented in large-scale studies.[1-19]

In this retrospective, multicenter study, the outcomes of older patients with CBF-AML were evaluated to reflect a real-life setting in the recent era.

Methods

We retrospectively reviewed 251 patients (≥60 years old), diagnosed with either t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22) between January 2000 and June 2019, who received intensive induction chemotherapy. Minimal required follow-up was 6 months in surviving patients. Twenty-two patients were excluded because of incomplete data regarding therapy or follow-up: therefore, the final analysis included 229 patients (Figure 1).

The Italian group conceived the concept of study, collected the data from participating centers anonymously and homogeneously with pre-determined variables. Consent to collect and use the medical records was obtained by local human research boards and the study was approved by the Institutional Review Board of Veneto Institute of Oncology (IOV).

AML was defined by the 2008 World Health Organization (WHO) diagnostic criteria[33] and updated versions. Fitness criteria for treatment with curative intent differed significantly between centers and years of treatment, as no universal standard was available.[10] All patients underwent thorough physical and laboratory evaluation of comorbidities and organ function according to each institution's clinical practice.

The primary CBF designation was made in all patients by means of karyotype, fluorescence *in situ* hybridization or molecular genetic testing. In molecular analysis, other common mutations in *KIT*, *FLT3*, *NPM1*, and *RAS* at diagnosis were collected when available. A complex karyotype was defined by three or more additional cytogenetic abnormalities. Patients with a serum creatinine two or more times higher the institutional upper limit of normal and/or creatinine clearance ≤50 mL/min were considered to have renal dysfunction. Complete remission was defined as bone marrow blasts <5%, absence of circulating blasts, and absence of extramedullary disease. Patients were categorized at high risk of relapse on the basis of adverse clinical or laboratory findings at diagnosis (hyperleukocytosis: ≥80x10^9/L white blood cells; extensive hepatic and/or splenic infiltration), failing to achieve CR after the first course of chemotherapy, and persistence of molecular transcripts at the end of planned consolidation.

First-line treatment

The induction regimens were highly heterogeneous but could be categorized into three major groups according to drug types and schedule: (i) "3+7" regimens, consisting of an anthracycline plus cytosine arabinoside; (ii) "3+7"-like regimens, which were a "3+7" regimen plus other drugs"; and (iii) "no anthracycline based regimen". These regimens are described in detail in the *Online Supplementary Data* section.

Following induction therapy, patients who achieved CR received consolidation (at least 1 cycle: range, 1-5) or maintenance treatment. The consolidation administered was also heterogeneous but mainly consisted of chemotherapy containing cytarabine at a dose of 9 g/m^2 or 18 g/m^2. Autologous HSCT performed in first CR (7 patients) was considered part of consolidation treatment. Of note, no patient underwent autologous HSCT after 2009.

All but four patients were treatment-naïve before intensive induction chemotherapy: the four patients who had received some treatment had been given only one cycle of an HMA with no response. We purposefully omitted patients who had been treated with multiple courses of HMA.

Hematopoietic stem cell transplantation

After induction and consolidation, allogeneic HSCT (15 patients) was performed, as mentioned above, in patients considered at high risk of relapse (with adverse clinical or laboratory findings at diagnosis) and in patients failing to achieve CR after the first course of chemotherapy (Figure 1). A reduced-intensity conditioning was used in all cases.

Study endpoints

The primary endpoints of the study were the objective response rate, defined as the percentage of patients achieving a CR following induction therapy, overall survival (OS), and event-free survival (EFS).

Secondary endpoints included analysis of: (i) biological and clinical baseline factors potentially affecting the primary endpoints; (ii) the impact on survival of therapeutic choices (induction and consolidation) made by the physicians during treatment; and (iii) role of age in defining differences among the series of patients using 70 years old as the cutoff.

Statistical analysis

According to the nature of the variables, Fisher exact and Pearson χ^2 tests were used to test the differences in proportions, and the Mann-Whitney and two-way Student *t* tests to compare nonparametric and parametric variables, respectively. The hypothesis of normal distribution was tested by the Shapiro-Wilk test. Differences were considered statistically significant for $P \leq 0.05$.

The impact of age and type of induction therapy on the overall response rate and on 30- and 60-day mortality was tested by Pearson χ^2 tests on actual results. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated with a logistic regression model.

In survival analysis, OS was defined as the time from diagnosis to death or last follow-up; disease-free survival was defined as the time from achievement of CR until relapse of leukemia, death or last follow-up; and EFS was defined as the time from diagnosis to any adverse event or last follow-up. Survival functions were calculated according to the Kaplan-Meier method, and differences tested by the log-rank test. The impact of single baseline covariates was tested in univariate analysis by Cox proportional hazard modeling and results compared by calculating the hazard ratio (HR) and corresponding 95% CI. We then chose to carry out multivariate analysis on EFS using factors for which the *P* value was ≤0.05 at univariate modeling.

Relapse mortality was defined as death due to leukemia relapse, and non-relapse mortality as death from any other cause in the absence of leukemia. Both were used as mutually exclusive competing events in the survival analysis. Cumulative incidence functions were compared using the Grey test.

To test the effects of allogeneic HSCT, we used a Mantel-Byar approach treating allogeneic HSCT as a time-varying covariate.

All analyses were performed using the Stata IC version 14.2 platform by StataCorp (College Station, TX, USA).

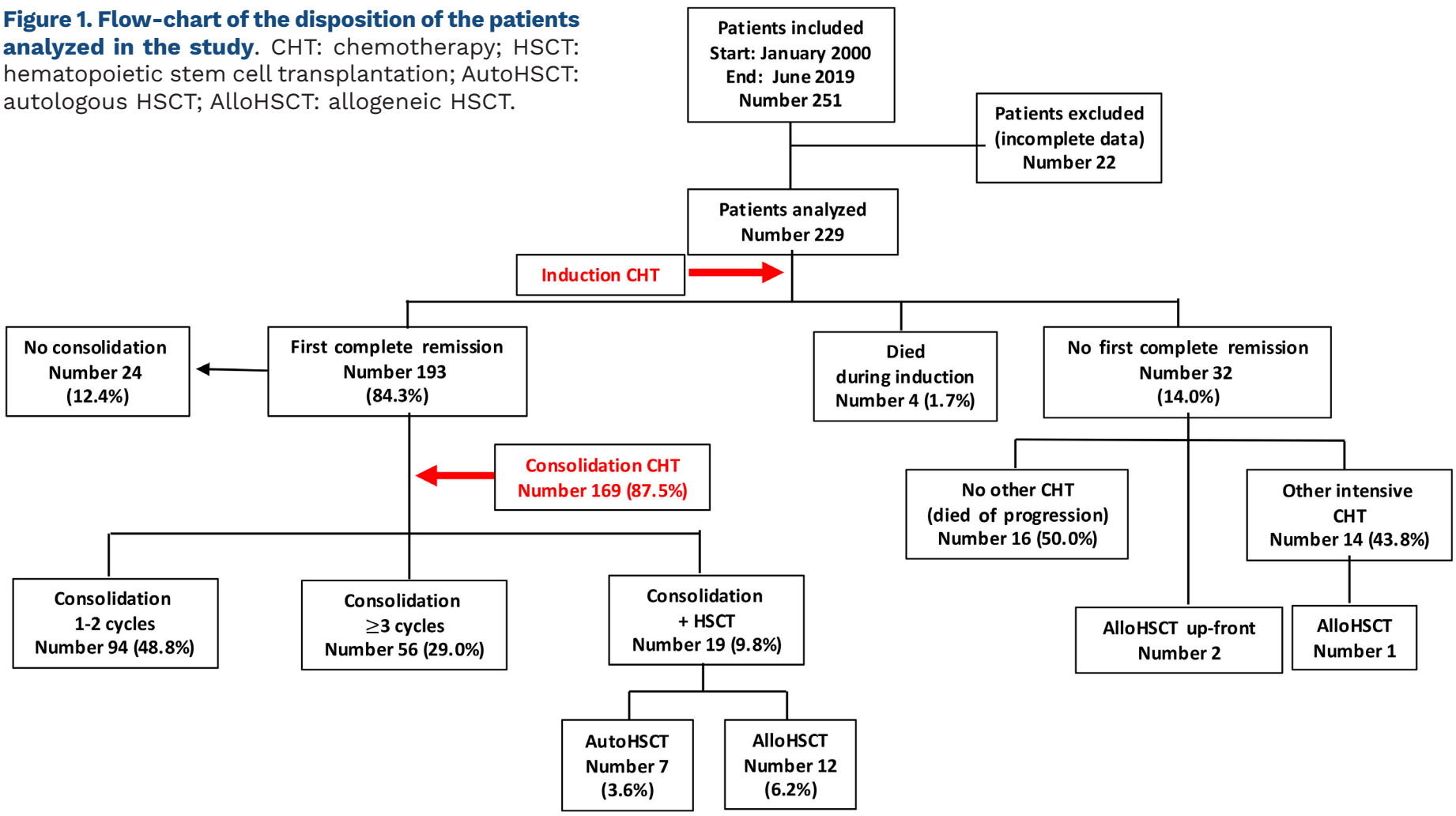


Figure 1. Flow-chart of the disposition of the patients analyzed in the study. CHT: chemotherapy; HSCT: hematopoietic stem cell transplantation; AutoHSCT: autologous HSCT; AlloHSCT: allogeneic HSCT.

Results

Patients

The patients' characteristics are shown in Table 1. The study included 229 evaluable patients, aged 60.0-84.4 years old (median: 66.2 years). Twenty-two patients (9.8%) had secondary AML (of whom 14 had prior myelodysplastic syndromes, the other 8 had therapy-related AML). Complete karyotype analysis was available at diagnosis for 115 patients (50.2%) (Tables 1 and 2): 34/115 (29.6%) had additional cytogenetic abnormalities other than the characteristic CBF translocations, and 7/115 (6.1%) had a complex karyotype. The patients' characteristics were similar between patients with t(8;21) and inv(16) AML, except for a higher white blood cell count at diagnosis in the case of inv(16) patients ($39.5x10^9$/L *vs.* $20.6x10^9$/L; *P*=0.002) (Table 1). For this study, we divided the whole series into two groups according to age, using 70 years as the cutoff. There were 59 patients above the age of 70 who were treated with intensive induction chemotherapy and multiple consolidation cycles or rescue chemotherapy (Table 2). No statistically significant differences in the main biological and clinical variables between age groups were observed (Table 2).

Induction treatment

Induction treatment is summarized in Table 3. The most frequently used induction regimens contained anthracycline (201 patients, 87.8%) (Table 3). There was a statistically significant difference in the use of an anthracycline during induction between age groups: more than 90.0% of patients <70 years old (155, 91.1%) were treated with an anthracycline compared to less than 80.0% in the older group (46, 77.8%) (OR=0.75, 95% CI: 0.47-1.84; *P*=0.04) (Table 3). The more common use of induction without an anthracycline in older patients (22.2% *vs.* 8.9%) (OR=0.75, 95% CI: 0.47-1.84; *P*=0.04) was likely due to fear of increased cardiac toxicity. Impressively, 193 patients achieved CR (84.3%) with no difference in CR rate between younger and older patients (146 [85.8%] *vs.* 46 [78.0%]) (OR=1.34, 95% CI: 0.87-2.84; *P*=0.204) (Table 3). The type of induction treatment affected CR rates in the whole series (from 86.0% to 67.9%) with a statistically significant difference in favor of anthracycline-based regimens (OR=0.94, 95% CI: 0.87-1.85; *P*=0.03) (Table 4). The trend in favor of anthracycline use was maintained for older patients (OR=1.4, 95% CI: 0.47-1.84, *P*=0.04) (Table 4). Overall, 30- and 60-day mortality rates were 3.5% (N=8) and 6.6% (N=15), respectively, with no statistical differences between the younger and older groups: 30-day mortality: 5 (2.9%) *versus* 3 (5.1%) (OR=0.55, 95% CI: 0.47-1.14; *P*=0.428) and 60-day mortality: 9 (5.3%) *versus* 6 (10.2%) (OR=1.55, 95% CI: 0.75-3.14; *P*=0.223) (Table 3).

Consolidation and transplantation

One hundred sixty-nine (87.5%) patients who achieved CR received consolidation (Figure 1, Table 3), without a statistically significant difference between age groups: 132 (89.7%) patients <70 years old *versus* 37 (80.4%) older pa-

Table 1. Characteristics according to core-binding factor translocation.

Characteristic	All patients N=229	t(8;21) N=92	inv(16) N=137	*P*
Age in years, median (range)	66.9 (60-84.4)	67.0 (60-84.4)	66.8 (60-79.6)	0.467
Patients ≥70 years, N (%)	61 (26.6)	23 (25)	38 (27.7)	0.698
Male/female, N/N	115/114	49/43	66/71	0.329
AML type, N (%) *De novo* Secondary Therapy-related	 184 (81.8) 22 (9.8) 19 (8.4)	 74 (80.5) 10 (10.8) 8 (8.7)	 110 (80.3) 12 (8.7) 11 (8.0)	0.892
Granulocytic sarcoma, N (%)	2/102 (1.9)	1 (1.1)	1 (0.7)	NA
WBC x10^9/L, median (range)	31.9 (0.5-417.0)	20.6 (1.2-417.0)	39.5 (0.5-270.0)	0.002
PB blasts >30%, N (%)	19/126 (15.1)	3/53 (5.7)	16/73 (21.9)	0.006
PB blasts >80%, N (%)	7/126 (5.6)	1/53 (1.9)	6/73 (8.2)	0.080
Platelets x10^9/L, median (range)	56.1 (2.0-419.0)	50.7 (5.0-331.0)	59.7 (2.0-419.0)	0.501
Platelets <20x10^9/L, N (%)	36/175 (20.6)	15/69 (21.7)	21/106 (19.8)	0.967
Hb g/dL, median (range)	8.6 (3.1-13.3)	8.7 (4.9-12.8)	8.4 (3.1-13.3)	0.349
Blasts in marrow >80%, N (%)	29/116 (25)	9/46 (19.6)	20/70 (28.6)	0.401
Elevated LDH, N (%)	73/100 (73)	26/40 (65.0)	47/60 (78.3)	0.170
Additional cytogenetic abnormalities, N (%)	34/115 (29.6)	10/46 (21.7)	24/69 (34.8)	0.239
Complex karyotype, N (%)	7/115 (6.1)	2/46 (4.3)	5/69 (7.2)	0.704
FLT3-positive, N (%)	19/150 (12.7)	4/57 (7.0)	15/93 (16.1)	0.224
NPM1-positive, N (%)	3/118 (2.5)	1/47 (2.1)	2/71 (2.8)	0.645
KIT-positive, N (%)	18/142 (12.7)	12/62 (19.4)	6/80 (7.5)	0.046
RAS-positive, N (%)	16/39 (41)	3/18 (16.7)	13/21 (61.9)	0.009

AML: acute myeloid leukemia; NA: not applicable; WBC: white blood cells; PB: peripheral blood; Hb: hemoglobin; LDH: lactate dehydrogenase.

tients (OR=1.8, 95% CI: 1.2-2.8; *P*=0.7). While no significant difference in number of patients consolidated with one or two cycles was observed between the age groups (45.7% *vs.* 58.7% in younger *vs.* older patients, respectively), as expected, fewer older patients (only 19.6%) were treated with multiple (≥3) courses as compared to patients <70 years old (32.0%), although the difference was not statistically significant (OR=0.8, 95% CI: 0.4-1.8; *P*=0.076). Consolidation therapy in CR included allogeneic HSCT in 12 patients. All patients who received a transplant (except 3) were aged ≤70 years. Reasons for proceeding to a transplant are listed in the Methods section. The individual characteristics and clinical history of patients undergoing transplantation as part of first-line treatment are provided in *Online Supplementary Tables S1* and *S2*. Twenty-four patients (12.4%) who achieved CR but did not receive intensive consolidation (chemotherapy and/or transplant) received maintenance right after induction with various agents, including low-dose cytarabine (N=20), azacytidine (N=3) and natural killer-cell infusions (N=1) (Figure 1).

Overall, disease-free and event-free survival

As of December 2019, 103 patients (45%) were still alive, with a median follow-up of 53.5 months (range, 6-181 months). One hundred twenty-six patients (55.0%) had died, in most cases from leukemia relapse/progression (87 patients, 69.0%).

Survival analysis was performed excluding patients with a complex karyotype (7 patients), as it was already shown that these patients do not benefit from the better survival associated with CBF-AML and therefore do not represent the prognosis of CBF-AML.

The OS was 50.2% (95% CI: 44.2-56.5) at 3 years, 45.0% (95% CI: 41.3-49.2) at 5 years and 36.7% (95% CI: 30.2-42.4) at 10 years (Figure 2A). As expected, no difference in OS was observed between patients treated in US or European centers: 5-year OS 51.5% (95% CI: 46.7-59.1) *versus* 43.2% (95% CI: 37.3-49.2), respectively (HR=0.67, 95% CI: 1.4-2.0; *P*=0.53). We also analyzed survival according to years of treatment, observing a statistically significantly difference: the 3-year OS for treatment years 2000-2009

Table 2. Characteristics according to age group.

Characteristic	All patients N=229	Aged 60-69 years N=170	Aged 70-85 years N=59	*P*
Male/female, N/N	115/114	88/82	27/32	0.427
AML type, 225 evaluated, N (%) *De novo* Secondary Therapy-related	 184 (81.8) 22 (9.8) 19 (8.4)	 137 (82.0) 18 (10.8) 12 (7.2)	 47 (81.0) 4 (6.9) 7 (12.1)	0.390
Hb, g/dL, median (range)	8.6 (3.1-13.3)	8.4 (3.1-12.8)	8.9 (5.4-13.3)	0.225
WBC x10^9/L, median (range)	31.9 (0.5-417)	30.6 (0.5-270)	35.7 (1.6-417)	0.519
Platelets x10^9/L, median (range)	56.1 (2-419)	54.2 (5-331)	61.2 (2-419)	0.458
PB blasts x10^9/L, median (range)	18.5 (0.0-243)	21.8 (0.0-243)	10.9 (0.0-61)	0.134
PB blasts >30%, N (%)	19/126 (15.1)	15/87 (17.2)	4/39 (10.3)	0.311
PB blasts >80%, N (%)	7/126 (5.6)	7/87 (8.0)	0/39 (0.0)	0.068
Blasts in marrow >80%, N (%)	29/116 (25.0)	22/85 (25.9)	7/31 (22.6)	0.716
Elevated LDH, N (%)	73/100 (73.0)	52/76 (68.4)	21/24 (87.5)	0.066
Renal insufficiency, N (%)	23/89 (25.8)	16/65 (24.6)	7/24 (29.2)	0.663
Additional cytogenetic abnormalities, N (%)	34/115 (29.6)	24/89 (27.0)	10/26 (38.5)	0.258
Complex karyotype, N (%)	7/115 (6.1)	4/89 (4.5)	3/26 (11.5)	0.186

AML: acute myeloid leukemia; Hb: hemoglobin; WBC: white blood cells; PB: peripheral blood; LDH: lactate dehydrogenase.

Table 3. Administered treatment according to age group.

Characteristic	All patients N=229	Aged 60-69 years N=170	Aged 70-85 years N=59	*P*
Induction therapy, N (%) "3+7" regimen "3+7" + other drugs No anthracycline	 100 (43.6) 101 (44.2) 28 (12.2)	 76 (44.7) 79 (46.4) 15 (8.9)	 24 (40.6) 22 (37.2) 13 (22.2)	0.04
Complete remission after induction, N (%)	193 (84.3)	147 (86.5)	46 (78.0)	0.204
Mortality, N (%) At 30 days At 60 days	 8 (3.5) 15 (6.6)	 5 (2.9) 9 (5.3)	 3 (5.1) 6 (10.2)	 0.428 0.223
Patients in remission, N (%) Not consolidated/only maintenance therapy after remission Consolidated with 1-2 cycles Consolidated with ≥3 cycles (but no transplant) Consolidated also with auto-transplant Consolidated also with allo-transplant	193 24 (12.4) 94 (48.8) 56 (29.0) 7 (3.6) 12 (6.2)	147 15 (10.2) 67 (45.7) 47 (32.0) 6 (4.0) 12 (8.1)	46 9 (19.6) 27 (58.7) 9 (19.6) 1 (2.1) 0 (0.0)	- - - 0.076 NA NA

NA: not applicable.

versus 2010-2019 was 47.1% (95% CI: 42.3-51.4) *versus* 54.7% (95% CI: 49.9-58.4), respectively (HR=1.28, 95% CI: 1.01-1.63; *P*=0.042). No difference in survival was observed for secondary CBF-AML since the 3-year OS was 50.0% (95% CI: 45.6-53.4) *versus* 48.0% (95% CI: 41.7-55.1) for *de novo versus* secondary CBF-AML, respectively (HR=1.3, 95% CI: 0.8-2.81; *P*=0.2).

The older patients experienced worse OS, with a 5-year OS of 48.5% (95% CI: 41.9-52.1) for patients <70 years *versus* 33.2% (95% CI: 28.1-36.4) for those ≥70 years (HR=1.6, 95% CI: 1.2-1.9; *P*=0.01) (Figure 2B). Non-relapse mortality also did not differ significantly between age groups: 25.1% (95% CI: 21.4-29.3) for patients <70 years old *versus* 27.2% (95% CI: 22.5-31.4) for older ones (HR=0.7, 95% CI: 0.3-1.7; *P*=0.472). However, it emerged from the analysis that there was higher leukemia-specific

Table 4. Achievement of complete remission according to type of induction therapy and age.

Induction therapy	Patients N (%)	CR N (%)	PR+NR+PD N (%)	Deaths N (%)	*P*
All patients					
"3+7"	100 (43.6)	86 (86.0)	11 (11.0)	3 (3.0)	-
"3+7" + other drugs	101 (44.2)	88 (87.1)	12 (11.9)	1 (1.0)	-
No anthracycline	28 (12.2)	19 (67.9)	9 (32.1)	0	-
Overall	229	193 (83.9)	32 (14.4)	4 (1.7)	0.03
Patients aged 60-69.9 years					
"3+7"	76 (44.7)	65 (85.6)	9 (11.8)	2 (2.6)	-
"3+7" + other drugs	79 (46.4)	70 (88.6)	9 (11.4)	0	-
No anthracycline	15 (8.9)	12 (80.0)	3 (20.0)	0	-
Overall	170	147 (85.9)	21 (12.3)	2 (1.8)	0.4
Patients aged 70-84.4 years					
"3+7"	24 (40.6)	21 (87.6)	2 (8.3)	1 (4.1)	-
"3+7" + other drugs	22 (37.2)	18 (81.9)	3 (13.6)	1 (4.5)	-
No anthracycline	13 (22.2)	7 (53.8)	6 (45.2)	0	-
Overall	59	46 (78.0)	11 (18.7)	2 (3.3)	0.04

CR: complete remission; PR: partial remission; NR: no response; PD: progressive disease.

mortality with increasing age: 37.5% (95% CI: 31.4- 43.1) in younger patients *versus* 51.5% (95% CI: 47.8-56.4) for patients ≥70 years (HR=1.1, 95% CI: 0.6-2.1; *P*=0.053). There was no significant difference in OS between CBF subtypes: the 3-year OS in patients with t(8;21) AML was 49.1% (95% CI: 45.4-53.5), whereas that of patients with inv(16) was 51.2% (95% CI: 48.3-55.4) (HR=0.87, 95% CI: 1.1- 2.1; *P*=0.427) (Figure 2C).

For the entire series, the 3-year and 5-year EFS rates were 36.9% (95% CI: 32.1-41.1) and 33.3% (95% CI: 29.2-37.1), respectively (*data not shown*), with no differences between those with t(8;21) or inv(16) AML (HR= 0.77, 95% CI: 0.4-1.7; *P*=0.64) (Figure 2C).

Achieving CR after induction therapy was the main factor affecting survival. Overall, a high CR rate following induction (84.3%) (Table 3) emerged from the analysis, regardless of age (OR=1.34, 95% CI: 0.87-2.84; *P*=0.204) (Table 3) and CBF subtypes (*data not shown*).

Overall, for the entire series, we observed 3-year, 5-year and 10-year EFS rates of 37.5% (95% CI: 34.2-41.5), 34.7% (95% CI: 30.1-39.2) and 26.9% (95% CI: 20.2-31.4), respectively, again with no differences between those with t(8;21) or inv(16) AML (Figure 2C).

Interesting, an improving EFS emerged when analyzing patients according to overall dose intensity (excluding patients submitted to allogeneic HSCT) with 3-year and 5-year EFS rates of 23.5% (95% CI: 19.9-27.1) and 19.5% (95% CI: 15.7-21.1) (without consolidation) to 29.6% (95% CI: 26.1-33.4) and 26.5% (95% CI: 22.4-29.9) (1-2 consolidation courses) to 55.0% (95% CI: 52.3-59.1) and 52.5% (95% CI: 47.8-56.4) (≥3 consolidation courses) (OR=9.34, 95% CI: 5.87-14.84; *P*<0.00001) (Figure 3A).

The same trend could be observed in both younger and older patients: patients <70 years had 5-year EFS rates ranging from 19.0% (95% CI: 13.1-23.4) to 49.0% (95% CI: 44.9-53.5) as they went from no consolidation to three or more consolidation cycles (OR=7.64, 95% CI: 3.85-13.64; *P*=0.00001) (Figure 3B). Patients >70 years old had slightly inferior 5-year EFS, ranging from 10.8% (95% CI: 7.8-13.6) (no consolidation) to 40.0% (95% CI: 34.8-44.1) (≥3 cycles), the latter with a median EFS of 11.8 months: 10 patients (Figure 3B). Concerning patients in CR after induction, analyzing the intensity of consolidation treatment among age groups (omitting allogeneic HSCT), a non-statistical but interesting trend (OR=0.8, 95% CI: 0.4-1.8; *P*=0.076) was still observed towards a lower number of cycles for older patients: 9/46 (19.6%) *versus* 47/147 (32.0%) for the group of patients receiving three or more cycles of consolidation courses (Table 3).

Rescue therapy after induction failure or relapse

Thirty-six patients did not achieve CR after induction: four (1.7%) died during the first cycle. Sixteen of the remaining 32 patients (50.0%) died with progression without further therapy; 14 (43.8%) received rescue chemotherapy and eight of these (57.1%) achieved CR: the last two patients went to transplantation without preceding chemotherapy (Figure 1). Overall, three patients underwent allogeneic HSCT: one after rescue chemotherapy and in CR, two as rescue up-front treatment without bridge therapy (Figure 1, *Online Supplementary Table S2*). In the whole series, 110 (48.0%) patients relapsed, with no difference between those with t(8;21) or inv(16) AML. The median disease-free survival was 20.8 (95% CI: 18.1-23.8) *versus* 16.3 months (95% CI: 13.4-20.2) for t(8;21) and inv(16) AML, respectively (HR=0.95, 95% CI: 0.4-1.9; *P*=0.754) (*data not shown*).

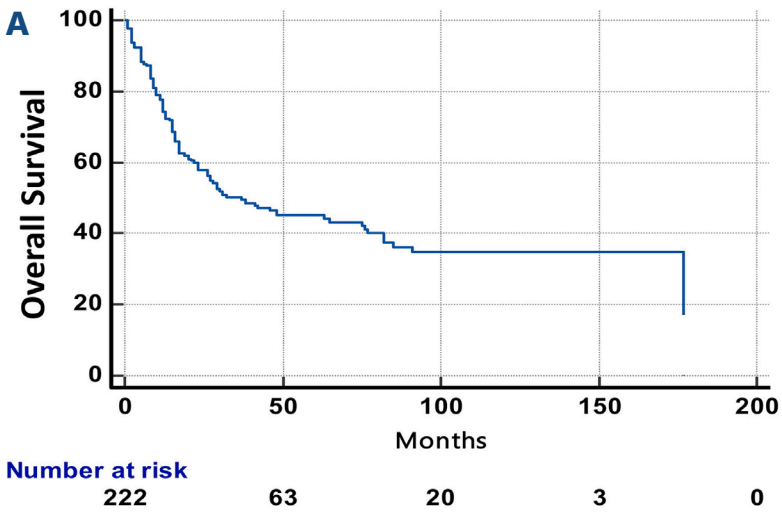
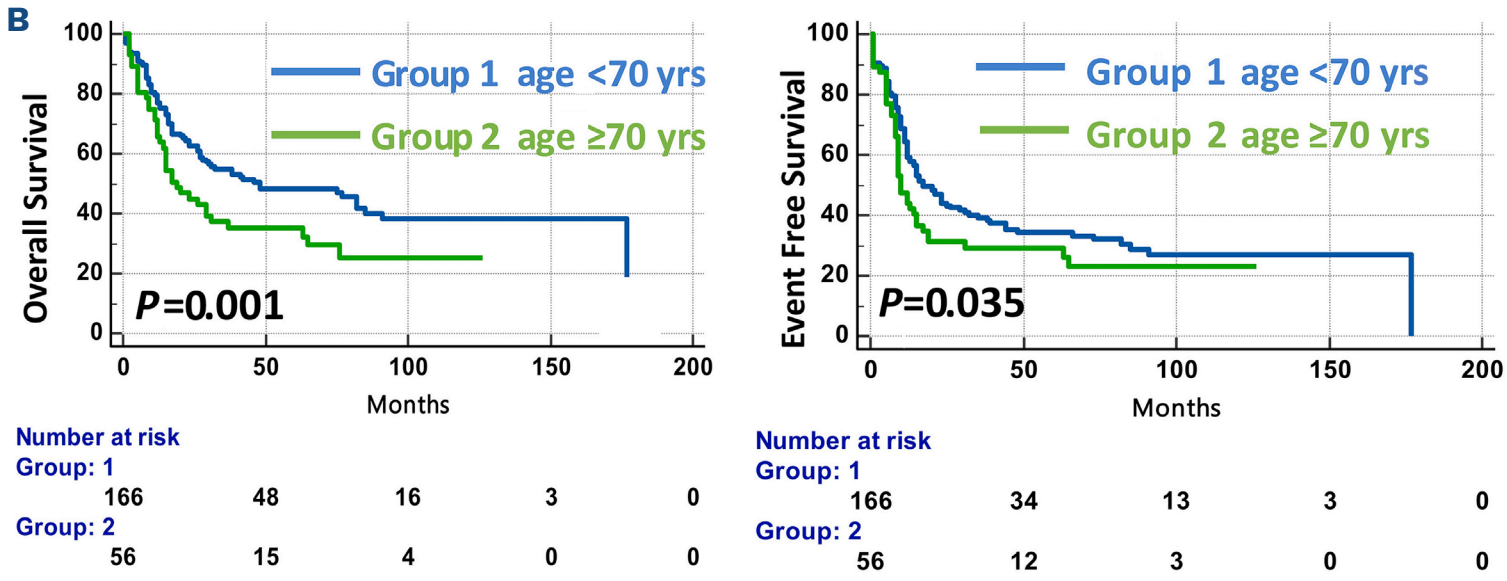
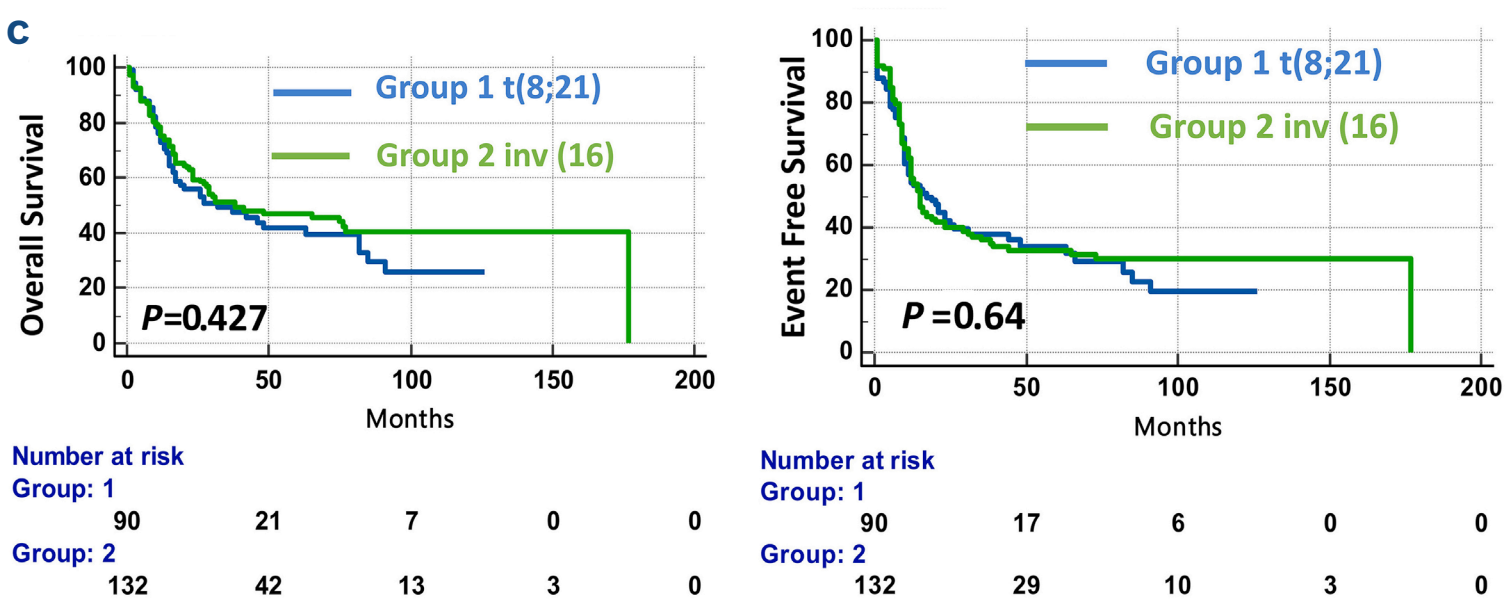


Figure 2. Overall survival and event-free survival according to age and core-binding factor translocation. (A) Overall survival of the whole study population. (B) Overall and event-free survival of patients divided according to age: <70 years *versus* ≥70 years. (C) Overall and event-free survival of patients divided according to core-binding factor translocation: t(8;21) *versus* inv(16).





Overall, 78 out of 110 patients (70.1%) received rescue treatment, and 58 of them (74.3%) achieved a second CR. Patients with inv(16) AML showed a nonstatistical trend towards a better chance of achieving second CR: 39 of 44 patients (88.6%) with for inv(16) AML *versus* 19 of 26 (73.1%) patients with t(8;21) AML (*P*=0.095).

Second-line allogeneic HSCT was the treatment of choice in all patients deemed fit for a transplant. All the 25 transplanted patients in this group (25 out of 78 patients, 32.0%) were rescued with chemotherapy before the transplant. An impressive advantage in survival was observed for transplantation *versus* conventional chemotherapy, with 3-year and 5-year OS rates of 62.7% (95% CI: 58.4-65.3) and 57.9% (95% CI: 54.4-60.2) *versus* 29.3% (95% CI: 26.4-32.5) and 19.3% (95% CI: 16.7-22.4) for transplant *versus* no transplant, respectively (HR=1.9, 95% CI: 1.4-2.1; *P*=0.001) (*Online Supplementary Figure S1*). Three (12.0%) transplanted patients died of disease progression; all the others (N=8, 32.0%) from toxicity. The median age of transplanted patients was 64.1 years (range, 60.7-74.8), with three patients over the age of 70 years and 12 over the age of 65 years.

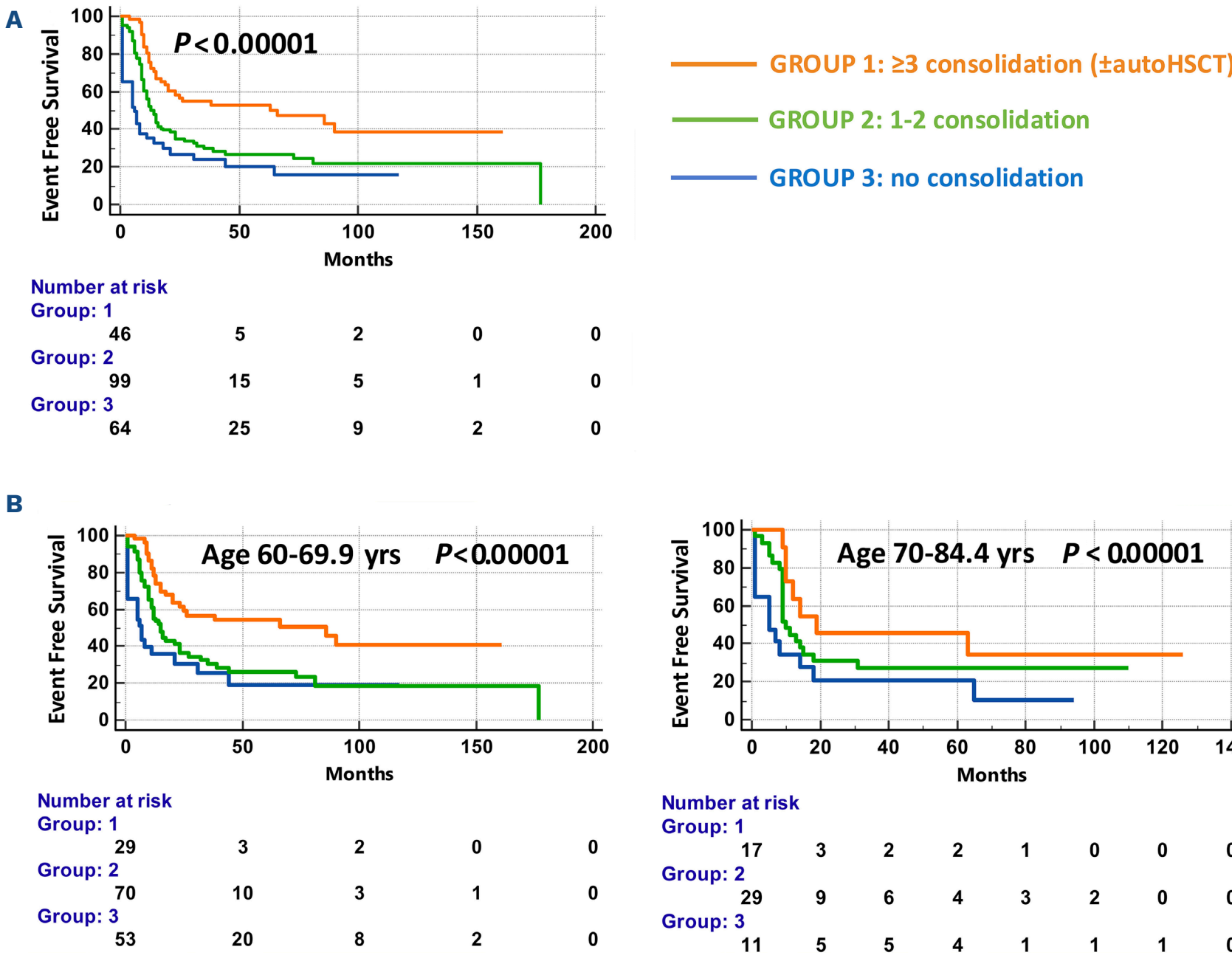


Figure 3. Event-free survival according to frontline treatment and age. (A) Event-free survival of patients divided according to frontline treatment. (B) Event-free survival of patients divided according to both frontline treatment and age (<70 years *vs.* ≥70 years). autoHSCT: autologous hematopoietic stem cell transplantation.

Univariate and multivariate analyses

In the univariate analysis for EFS (Table 5), age (≥70 years) (HR=1.78, 95% CI: 1.15-2.54; *P*=0.008), failure to achieve CR following induction (HR=8.96, 95% CI: 5.40-13.18; *P*<0.0001), absence of consolidation therapy (HR=0.75, 95% CI: 0.47-1.84; *P*=0.04) and fewer than three consolidation courses (including autologous HSCT) (HR=9.57, 95% CI: 5.6-13.4; *P*<0.001) identified patients at higher risk of poor survival. Inclusion of an anthracycline in the induction course also approached statistical significance for a better EFS (HR=1.06, 95% CI: 0.14-2.08; *P*=0.05).

In multivariate analysis failure to achieve CR following induction (HR= 8.99, 95% CI: 3.78-16.66; *P*<0.001) and fewer than three consolidation courses (HR= 7.99, 95% CI: 3.18-15.7; *P*<0.001) remained independent predictors of poorer EFS (Table 5).

Univariate analysis for EFS according to cytogenetic and molecular biology (mutated *FLT3*-ITD and TKD; *NPM1*, *NRAS* and *KRAS*, *KIT* D816V) was performed only for patients with available data: only the presence of mutated *KIT* D816V at diagnosis identified patients with poor EFS (HR= 6.85, 95% CI: 3.42-11.71; *P*=0.04) (*Online Supplementary Table S3*).

Discussion

In our study of 229 patients with long-term follow-up, intensive induction and consolidation provided long-term EFS with low transplant-related mortality. During induction, we observed that older patients with CBF-AML respond favorably to intensive treatment with anthracyclines resulting in high CR rates. Moreover, according to both univariate as well as multivariate analyses, achievement of CR was one of the most important factors for having long-term EFS.

In terms of consolidation, our study showed that three or more courses of consolidation (in 7 cases including autologous HSCT) were associated with longer EFS. Previously published studies have shown that approximately 60% of older patients could not receive three or more cycles of consolidations[28,34-40] but, when received, this was associated

Table 5. Univariate and multivariate analyses for event-free survival.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Male sex	1.31	0.81-2.84	0.29	-	-	-
Secondary/therapy-related AML	0.93	0.66-1.06	0.4	-	-	-
Age ≥70 years	1.78	1.15-2.54	0.008	1.68	0.85-2.84	0.137
CBF type	0.74	0.50-1.21	0.437	-	-	-
WBC at diagnosis ≥20x10^9/L	0.8	0.45-1.4	0.45	-	-	-
WBC at diagnosis t(8;21) ≥20x10^9/L	0.9	0.55-1.5	0.6	-	-	-
WBC at diagnosis inv(16) ≥20x10^9/L	0.55	0.25-1.1	0.4	-	-	-
Failure to achieve CR after induction therapy	8.96	5.5-13.8	<0.0001	8.99	3.78-16.66	<0.001
Allogeneic HSCT during first-line	0.92	0.38-1.85	0.700	-	-	-
>1 cycle needed to achieve CR	1.59	0.73-3.50	0.246	-	-	-
Absence of consolidation therapy	0.75	0.47-1.84	0.04	0.35	0.13-2.96	0.4
1-2 cycles for consolidation	1.48	0.75-3.20	0.276	-	-	-
≥3 cycles for consolidation including autologous HSCT	9.57	5.6- 13.4	<0.0001	7.99	3.18-15.7	<0.001
No anthracycline in induction	1.06	0.14-2.08	0.05	0.45	0.23-1.96	0.26

HR: hazard ratio; 95% CI: 95% confidence interval; AML: acute myeloid leukemia; CBF: core-binding factor; WBC: white blood cells; CR: complete remission; HSCT: hematopoietic stem cell transplantation.

with a longer survival.[40] These outcomes may be due to general improvements in the treatment options for elderly AML patients[16-18,34-42] and to a reduction of transplant-related mortality following induction chemotherapy.[28,35] It could also reflect the biological features of CBF-AML, in which the marked sensitivity of blasts and leukemic stem cells to chemotherapy provides better results.[36] Some other studies also demonstrated that CBF-AML patients can achieve long-term remission and functional cure after fixed-term chemotherapy also at advanced age.[2,40,41]

HMA with Bcl2 antagonists (e.g., venetoclax) have been increasingly used in older patients with AML, or in patients with medical conditions that prevent the use of standard intensive chemotherapy. These agents are considered less toxic than conventional chemotherapy, are associated with lower 28-day transplant-related mortality, are very active in favorable-risk AML and have provided a survival advantage as compared to other treatments in registration trials as well as real-life experience.[16,17] Nevertheless, they have been tested only in a population of older patients defined as unfit for intensive chemotherapy when applying currently available fitness scores. Furthermore, even though results in this setting of unfit patients have been consistentently better than those with low-to-intermediate intensity chemotherapy,[16] especially in the context of upfront treatment[17,37,38] and adverse cytogenetics,[37,39] they still appear as a non-curative approach, requiring continuous treatment until disease progression, while long-lasting remissions are rare. In the setting of CBF-AML there are limited and conflicting data about the efficacy of HMA plus venetoclax since patients with CBF-AML have been excluded from most venetoclax-based studies. Zhang *et al*. reported the largest series (30 patients) involving HMA plus venetoclax in CBF-AML. The median duration of follow-up for the entire cohort was 11.6 months and the 2-year probability of OS was 92.2%, with a trend toward a better 2-year OS in patients with inv(16)/t(16;16) compared to those with t(8;21) (100% *vs.* 81.5%; *P*=0.09).[43] Hang *et al*. reported on 58 consecutive patients with CBF-AML treated with intensive chemotherapy (49 patients) or HMA plus venetoclax (9 patients), showing a superior outcome for patients treated with intensive chemotherapy (CR rate 25.0% *vs.* 91.3%, respectively; *P*=0.007).[44] These results were confirmed by Zhou *et al*. in 106 CBF-AML patients treated with various regimens of intensive chemotherapy (97 patients) or HMA plus venetoclax (9 patients): the median EFS ranged from 7.9 to 10.9 months in the intensive chemotherapy groups *versus* 3.5 months in the HMA plus venetoclax group.[45]

In our analysis, we found that the presence of high tumor burden (high white blood cell count or hepatosplenic involvement) had no impact on the achievement of CR or survival (*data not shown*), as has been reported by others.[19,25,26,40,41,46]

Relapses have been reported to occur in up to 35.0% of any-aged CBF-AML patients.[49] In our series, comprising only an older population, 110 (48.0%) patients relapsed, with no difference between those with t(8;21) or inv(16). Overall, 78/110 relapsed patients (70.1%) received rescue

treatment, with a high rate of second CR (74.3%) achieved. Patients with inv(16) AML showed a non-statistical trend towards a better chance of achieving a second CR: 88.6% (inv16) *versus* 73.1% for t(8;21) AML (*P*=0.095).

There is no established salvage treatment for patients with relapsed CBF-AML. In a retrospective analysis by the French AML Intergroup concerning 145 patients in first relapse, patients who received gemtuzumab ozogamicin (GO)-based chemotherapy followed by allogeneic HSCT had a significantly higher 5-year disease-free survival (83.0%) than those who received conventional chemotherapy (44.0%) (*P*=0.01). It was concluded that GO combined with chemotherapy and transplantation is safe and efficient.[48] This study has some limitations due to an inadequate number of patients to assess the efficacy and safety of GO upfront or in a relapsed setting.

In our series only four patients received GO induction-based chemotherapy: they were all treated after 2017, when GO received Food and Drug Administration (FDA) re-approval for the first time in newly diagnosed AML patients. A meta-analysis of five randomized trials showed that the addition of GO to remission induction therapy improved survival in CBF-AML, with an absolute survival benefit of 20.7% (OR=0.47, 95% CI: 0.31-0.73; *P*=0.0006).[49] Borthakur *et al*. reported 3-year OS and relapse-free survival rates of 85.0% and 78.0%, respectively, in a study of FLAG-GO (fludarabine, cytarabine, granulocyte colony-stimulating factor plus GO) in CBF-AML,[50] concluding that the incorporation of GO into remission induction should be considered standard for CBF-AML.[51] Our series included patients treated from 2000 to 2019 and this could explain why only four patients were treated with GO: from 2000 to 2010 GO had first FDA approval for relapsed AML patients not eligible for intensive chemotherapy; only in the second FDA approval (2017) were newly diagnosed CD33-positive AML patients included. Furthermore, the use of GO in elderly patients is limited due to fear of drug-related toxicity. In older patients, this could probably be modulated by reducing the drug dose and/or the number of GO administrations.

We observed an impressive advantage in survival for patients in second CR (78 patients) who underwent allogeneic HSCT (25 patients) compared to those rescued only with conventional chemotherapy (53 patients). These data regarding transplant in second line confirm the feasibility and efficacy of the procedure also in older patients. Despite this, transplant in older patients is not widely used: worldwide, fewer than one-third of patients aged 60-70 years old ever undergo a transplant and only 7.0% of those aged 70-75 years are transplanted. Considering the constant progress in transplant technologies over the last two decades, a more careful evaluation of patient's fitness is needed in order not to exclude patients for a transplant procedure solely based on an age above 65 years.

We acknowledge several limitations of our study. The first regards molecular data, which were incomplete, as the range of depth of analysis now allowed by next-generation genomics was unavailable at the time of treatment, and in the case of established markers such as *KIT*, *FLT3*, *NPM1* and *RAS*, data were related to more recent years. Second, minimal residual disease monitoring, a cornerstone of the current treatment of CBF-AML, was available only in a minority of the patients of our series, not allowing conclusions to be drawn regarding its predictivity in term of OS, as reported in literature.

Nevertheless, it is unlikely that a prospective study will ever be conducted on this topic, and the consistency of the chemotherapeutic regimens applied over the last two decades in the treatment of AML, as well as the size of our final database and the very long follow-up at our disposal, still enabled us to draw important long-term conclusions from the results.

In summary, data emerging from our analysis indicate that, due to the "biological fitness" related to the high chemosensitivity of CBF blasts and leukemic stem cells, patients with CBF-AML can be intensively treated, with a significant chance of cure, up to a very advanced age, also including, in selected cases, allogeneic HSCT when indicated, without a high rate of toxicity. Although HMA plus venetoclax combinations appear to be very effective and safe treatments, the optimal therapy for a patient is currently unknown, given the lack of prospective comparisons in CBF-AML. The risk and benefit of each approach should be tailored for an individual patient; however, our study clearly shows that patients with CBF-AML should not be excluded from receiving intensive therapies based solely on age.

Disclosures

No conflicts of interest to disclose.

Contributions

FM conceived and designed the study, provided study patients, collected, assembled, analyzed and interpreted data, and wrote the manuscript. MG conceived and designed the study, provided study patients, analyzed and interpreted data, and wrote the manuscript. AS collected, assembled, analyzed and interpreted data, and wrote the manuscript. EB, ML, JCB, CP, CT, FFe, GM, RC, EAM, CG, CCSY, HJD DC, AC, JRG, ML, SP, FL, SG, FFo, AV, MF, EA, DM, GMR, GR, EDB, GV, FA, A-KE, PV, GH, GB, MK, GM and NK provided study patients. All authors reviewed and approved the final manuscript. FM and MG are responsible for all aspects of the work.

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Data-sharing statement

Data may be available upon contacting the corresponding authors.

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