Feasibility and results of autologous stem cell transplantation in *de novo* acute myeloid leukemia in patients over 60 years old. Results of the CETLAM AML-99 protocol

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A B S T R A C T

Background and Objectives. The benefits of high-dose cytarabine, anthracyclines and hematopoietic stem cell transplantation in the treatment of acute myeloid leukemia (AML) are greater in younger rather than in older patients. We assessed the proportion of patients over 60 years with *de novo* AML who qualified for intensive therapy and determined the feasibility and results of autologous stem cell transplantation (ASCT) in first complete remission (CR).

Design and Methods. Induction therapy included idarubicin, cytarabine and etoposide. Patients who achieved CR received one cycle of mitoxantrone and cytarabine and ASCT as consolidation therapies.

Results. Over a 4-year period, 258 patients were registered of whom 135 (52%) were enrolled for intensive treatment. The CR rate was 61%, advanced age (p=0.033) and unfavorable cytogenetics (p=0.015) emerged as independent negative prognostic factors for CR. The 2-year overall survival (OS) was 23% (CI 14%-30%) and was poorer in patients with unfavorable cytogenetics (p=0.035), age over 70 years (p=0.019) or leukocytosis (p = 0.006). Only 27% of the potential candidates underwent ASCT. The probability of 2-year leukemia-free survival after consolidation was 39% (CI 6%-71%) for these patients and 22% (CI 6% - 39%) for candidate patients not undergoing ASCT (p=0.07).

Interpretation and Conclusions. Over 25% of the patients 60 to 70 years with *de novo* AML benefit from standard intensive treatment. In these patients, ASCT has a tolerable toxicity and may have a positive impact on leukemia-free survival.

Key words: acute myeloid leukemia, elderly patients, autologous stem cell transplantation, survival.

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Intensive induction and consolidation therapy with agents such as idarubicin[1,2] and high-dose cytarabine[3-6] and hematopoietic stem cell transplantation[7] are the mainstay in the treatment of acute myeloid leukemia (AML). However, while the incidence of AML increases with age, these treatments provide greater benefit to younger rather than to older patients. More than one half of the patients with AML are older than 60 years[8] and, therefore, most are not candidates for intensive therapies because of co-morbid conditions or impaired general status. In patients fit enough for treatment, other factors contribute to a poorer outcome. These factors include a lower tolerance to prolonged pancytopenia and intensive therapy,[9,10] resulting in a higher mortality during induction, and a higher frequency of AML with poor-risk features such as poor-risk karyotypes, previous myelodysplastic syndrome (MDS) and multidrug resistance (MDR) phenotype, all resulting in a higher resistance to chemotherapy.[11,12] Anthracycline and cytarabine regimens in patients over 60 years old result in complete remission (CR) rates lower than 50% and long-term survival rates of about 10%.[11,13] Improved supportive therapy (i.e. new antibiotic and antifungal agents and growth-factors) and the invariably poor prognosis of patients treated with non-intensive therapies may have diminished the reluctance to expose elderly patients to intensive antileukemic schedules. However, the proportion of patients entered into clinical trials is usually not reported and the results may reflect the effect of selection rather than therapy.

The Catalan Group for the Study of Acute Leukemias and Myelodysplastic Syndromes

(CETLAM) conducted an open, non-randomized clinical trial including idarubicin, etoposide and cytarabine as an induction regimen followed by mitoxantrone and cytarabine-containing post-remission therapy. Patients completing consolidation were evaluated to proceed to autologous stem cell transplantation (ASCT). Regardless of whether they qualified to enter the study all patients diagnosed with AML during the study period were registered to assess the proportion of patients fit for treatment. The primary objectives were to determine the effectiveness of a chemotherapeutic schedule including standard induction therapy followed by one consolidation cycle, and to evaluate the feasibility, toxicity and results of ASCT in patients over 60 years with *de novo* AML in first CR.

Design and Methods

Eligibility

Patients 60 years of age or older with a morphologically confirmed diagnosis of AML,[14] except for acute promyelocytic leukemia, were eligible for this study.[15] Patients with AML arising after a previous diagnosis of MDS[14] or with secondary AML (i.e. after prior chemotherapy, radiotherapy or both) were excluded. According to ECOG criteria patients were required to have performance status 0-3. Patients with severe organ dysfunction not related to AML or a left ventricle ejection fraction lower than 50%, as measured by either multigated cardiac blood pool (MUGA) scan or echocardiography, were also excluded. Informed consent in accordance with local institutional committee criteria was required. All excluded patients diagnosed with AML in the participating centers during the study period were registered to assess the proportion of patients who qualified for intensive therapy.

Study design

Patients qualifying for intensive therapy received idarubicin 10 mg/m^2 intravenously on days 1, 3 and 5, cytarabine 100 mg/m^2 daily as a 24-hour continuous intravenous infusion on days 1 through 7 and etoposide 100 mg/m^2 intravenously over 30 minutes daily on days 1 through 3. A bone marrow aspirate was obtained when peripheral blood hematologic recovery was observed or on day 28. If the marrow blast percentage was lower than 5% the patient was considered in CR, and if the marrow blast percentage was higher than 5% but less than 50% of the marrow blast percentage at diagnosis the patient was considered in partial remission (PR) and received a second cycle of induction with the same drugs at the same doses. Patients who did not achieve PR were considered refractory and received salvage or no therapy. Treatment with colony-stimulating factors was not permitted. Guidelines for transfusion support and antimicrobial and antifungal prophylaxis or treatment were not given and the patients were included in institutional protocols of the participating centers.

Patients who achieved CR after 1 or 2 cycles of induction chemotherapy received one cycle of consolidation therapy (C1), consisting of mitoxantrone 12 mg/m^2 intravenously on days 5 and 6 and cytarabine 500 mg/m^2 every 12 h as a 2-hour intravenous infusion on days 1 through 6. Patients who had unacceptable toxicity during or after induction therapy or after consolidation therapy were considered ineligible for ASCT and did not receive further therapy. A performance status score < 3, serum liver enzymes and bilirubin lower than twice the upper limit of normality and a MUGA scan demonstrating a left ventricle ejection fraction higher than or equal to 50% were required to qualify for ASCT. If ASCT was indicated, peripheral blood stem cells were collected as soon as possible after consolidation. Mobilization treatment consisted of 10 μg/kg of granulocyte colony-stimulating factor (G-CSF) every 12 h followed by collection from day 4. A minimum collection of 2×10^6 peripheral blood CD34$^+$ cells per Kg in an unmanipulated product was required to proceed to ASCT. If the first mobilization attempt failed, other sources of stem cells or mobilization procedures were allowed following the institutional protocols of the transplant units concerned. Conditioning regimens were cyclophosphamide 60 mg/kg/day intravenously on two consecutive days and total body irradiation (TBI) 13 Gy in 4 to 8 fractions, or alternatively, cyclophosphamide at the same dose and busulphan 1 mg/kg every 6 hours for 4 consecutive days. Intrathecal treatment was two doses of 12 mg of methotrexate on days -7 and -3. Isolation measures and prophylaxis and treatment of infections were carried out according to institutional protocols.

Definition of outcomes

Complete and partial remissions were defined as described above.[15] Patients who failed to achieve CR after one or two induction cycles were classified as having resistant disease (RD). Induction-related deaths (IRD) were defined as deaths during the period between the onset of therapy and the documentation of CR or recovery from aplasia with resistant disease. Overall survival (OS) was measured from the date of diagnosis until death from any cause or censored at the date of last contact for patients last known to be alive. Leukemia-free survival (LFS) was measured from the date of CR until relapse or death from any cause or censored at the date of last contact for patients last known to be alive and in first CR. Hematologic toxicity after cycles and after ASCT was measured as days to neutrophil recovery to > 0.5×10^9/L and days to platelet recovery > 20×10^9/L in 2 consecutive measurements

without transfusion support. Patients who died while neutropenic or thrombocytopenic were excluded from the analysis of hematologic toxicity. Remaining toxicities were defined and graded according to the WHO scales of toxicity.[16]

Statistical methods

Patients were stratified by age (60-70 years and over 70 years). Prognostic factors for CR, RD, and IRD rates were analyzed using Fisher's exact test and logistic regression analysis.[17] The distribution of OS and LFS was estimated by the Kaplan-Meier method.[18] Cox proportional hazards regression[19] was used to compare survival according to age group and to disease characteristics. A secondary landmark analysis for comparison of outcomes was performed between patients intended to undergo ASCT who finally received transplantation and those who did not for reasons other than early relapse or previous toxicities. All test results are reported using 2-sided *p* values and 95% confidence intervals (CI).

Results

Accrual and characteristics of patients

A total of 258 patients from 11 institutions were registered between June 1998 and December 2002. Of this total, 119 patients were ineligible for intensive treatment because of a previous diagnosis of MDS (n = 21), diagnosis of acute promyelocytic leukemia (n = 2), other previous or associated neoplasm (n = 10), severe associated illness or insufficient performance status (n = 66), very advanced age (n = 9), lack of family or social support (n = 8) and patients' refusal of intensive treatment (n = 3). Four patients followed and completed the intensive treatment schedule despite being excluded (1 with a previous MDS diagnosis and 3 with a prior neoplasm). Of the 135 eligible patients (52%), 110 (81%) were under 70 years of age, thus 76% of patients from 60 to 70 years were treated intensively while only 32% of patients over 70 years were. None of the 37 registered patients over 80 years received intensive therapy. The characteristics of the treated and untreated patients and their diseases are shown in Table 1. Untreated patients were older ($p<0.001$) and had a worse performance status ($p<0.001$). In addition, the proportion of untreated patients with trilineage dysplasia (20%) was higher than that of the treated patients (9%) ($p=0.001$). Cytogenetic results were not available for 20 (15%) patients qualified for intensive therapy, either because evaluable studies were not obtained (n = 14) or because metaphases were insufficient or information was inconsistent (n = 6). Among the 115 treated patients with evaluable cytogenetic data, 52% had normal karyotypes. Cytogenetic studies were not performed in almost 50% of patients reported but considered unfit for intensive treatment.

Response to induction therapy

As shown in Table 2, 82 (61%) patients achieved CR, 9 of whom (11%) required 2 courses of induction therapy. The rate of PR to the second induction course was 70% (9/13). Among patients not achieving CR, 20 (15%) had RD following one (n = 16) or 2 (n = 4) courses of induction therapy and 33 (24%) died during induction aplasia due to infection (n= 27) or major toxicity (n= 6). IRD was significantly more frequent in individuals with leukocytosis > 50×10^9/L ($p=0.045$); in fact, 10/25 (40%) of patients with leukocytosis died during induction therapy while the rate for patients without this feature was 21%. In patients surviving induction cytopenias, RD was strongly associated with poor risk cytogenetics; in fact 10/20 patients (50%) with poor risk cytogenetics had RD versus 9/67 (13%) of those with good or intermediate risk cytogenetics ($p=0.001$). RD was present in 6/17 patients over 70 years (35%) and in 14/85 (16%) younger patients, but this difference did not reach statistical significance ($p=0.074$). The responses to induction chemotherapy, according to selected clinical and disease characteristics, are shown in Table 3. On univariate analysis the CR rate was significantly lower for patients with unfavorable cytogenetics ($p=0.004$). The 64% CR rate among the 110 patients under 70 years differed with a borderline significance from the 44% rate among the 25 older patients ($p=0.058$). Trilineage dysplasia, leukocytosis and morphologic or phenotypic subtype of AML were not found to be associated with a lower CR rate. However, on multiple logistic regression analysis (Table 4), advanced age ($p= 0.033$) along with bad risk cytogenetics ($p= 0.015$) had an independent, statistically significant prognostic association with CR rate.

Post-remission therapy and autologous stem cell transplantation

Of the 82 patients who achieved CR, 7 (9%) did not receive the consolidation cycle of therapy. The reasons for withdrawing from further treatment included unacceptable toxicity of induction therapy (n = 5), the patient's decision to abandon treatment (n=1) and relapse before consolidation (n = 1). Among the 75 patients who received the consolidation cycle (91% of those having achieved CR), there were 9 consolidation-related deaths and 6 other patients had consolidation toxicities that disqualified them for ASCT. The remaining 60 patients (73% of those having achieved CR) were considered potential candidates for ASCT.

Finally, 16 patients (27% of the potential candidates) were submitted to ASCT. The median age of these patients was 64 years (range 61 - 70). The rea-

Table 1. Characteristics of patients according to qualification for intensive treatment.

	Excluded patients (N=123)	*Intensive treatment (N=135)*	*p value**
Patients' characteristics	*N (%)*	*N (%)*	
Male	68 (55)	71 (53)	NS
Age			
60 to 69 years	34 (28)	110 (81)	< 0.001
70 to 79 years	52 (42)	25 (19)	
0ver 80 years	37 (30)		
ECOG score 0 - 1	29 (24)	79 (59)	< 0.001
AML morphology**			
FAB M1-M2	26 (21)	61 (45)	
FAB M4 - M5	36 (29)	49 (36)	
Other FAB subtypes	11 (9)	9 (7)	
Trilineage dysplasia	25 (20)	12 (9)	0.001
Unclassified	25 (20)	4 (3)	
AML cytogenetics (MRC criteria)***			
Unfavorable	20 (16)	28 (20)	NS
Normal	29 (24)	60 (44)	
Other intermediate	11 (9)	22 (16)	
Favorable	2 (2)	5 (4)	
Not performed/ inadequate	61 (49)	20 (15)	

*ECOG: Eastern Cooperative Oncology Group. ** FAB:[20] French-American-British. 'Other FAB subtypes' includes immunophenotypically well defined M0, M6 and M7 subtypes and excludes AML with trilineage dysplasia or unclassifiable AML. *** MRC:[21] Medical Research Council.*

Table 2. Response to induction and consolidation therapy of the 135 intensively treated patients.

Induction treatment	*135 (52% of registered patients)*
Death during aplasia	33
Resistant disease	20 (16 after 1 cycle /4 after 2 cycles)
CR	82 (61% of treated patients, in 1 cycle: 73)
Withdrawal after induction	6 (induction toxicity 5, patient decision 1)
Relapse after induction	1
Consolidation treatment	75
Death during aplasia	9
Abandon after consolidation	6
Eligible for ASCT	60 (73% of patients achieving CR)
Relapse before mobilization	9
No mobilization	10
Patients' refusal of ASC	3
Not indicated by attending physician	22
ASCT performed	16 (27% of candidates)
Transplant-related mortality	3 (graft failure 2, infection 1)
Relapse after ASCT	5
Alive in CR after ASCT	8 (50% of patients receiving ASCT)

CR: complete remission. ASCT: autologous stem-cell transplant.

Table 3. Response to induction chemotherapy, according to selected clinical and disease characteristics.

Characteristics	*CR (%)*	*p value*
Cytogenetic group*		
Favorable/intermediate	58/87 (67%)	0.004
Bad risk		
10/28 (36%)		
Age (years)		
< 70 years	71/110 (64%)	0.058
70 years	11/25 (44%)	
Leukocytes ($\times 10^9$/L)°		
<50	70/110 (64%)	NS
>50	12/25 (48%)	
Trilineage dysplasia		
No	72/119 (61%)	NS
Yes	8/12 (67%)	

**Medical Research Council criteria.[21] °Not significant with other cut-off values either.*

sons for withdrawal from ASCT were insufficient mobilization of hematopoietic progenitors (n =10), early relapse (n =9), adverse medical advice (n=22) and patients' refusal (n=3). Only 1 of the 9 potential candidates for ASCT over 70 years actually underwent the procedure, 2 refused and 6 received adverse mediacal advice. Adverse medical advice was significantly more frequent in hospitals that had to refer the patients to an external transplant unit (10/14) than in those with in-hospital transplant units (12/46) (p=0.005). Stem-cells were mobilized from peripheral blood (in 13 patients), obtained from bone marrow (in 2) or both (in 1). The median time from diagnosis to ASCT was 4.5 months (range 3 to 10 months). The conditioning regimen was TBI and cyclophosphamide in 6/16 cases and busulphan and cyclophosphamide in the remaining cases; the median number of $CD34^+$ cells infused was 3×10^6/kg (range 2-13).

Overall survival

The median OS of untreated patients was 2 months with 4% of patients surviving at 1 year. Of the 135 treated patients, 106 (79%) had died by the time of analysis. The median follow-up for the remaining 29 was 15 months (range 6 to 62 months). The median survival of treated patients after diagnosis was 8 months (CI 5-12 months) and the estimated probability of 2-year survival was 23% (CI 14-30%) (Figure 1). For the 16 patients submitted to ASCT, the median survival after ASCT was 28 months (CI 8-49 months) and the estimated probability of 2-year survival after ASCT was 47% (CI 4-77%).

OS decreased significantly with advanced age (p=

Table 4. Multivariate analysis of factors associated with achievement of complete remission (CR) and overall survival (OS).

*CR**	*β*	*OR*	*95%CI OR*	*p value*
Bad risk cytogenetics	-1.14	0.32	0.13 - 0.80	0.015
Age > 70 years	-1.13	0.32	0.12 - 0.91	0.033
OS°	*β*	*OR*	*95%CI OR*	*p value*
Bad risk cytogenetics	0.53	1.70	1.04 - 2.79	0.035
Age > 70 years	0.68	1.97	1.12 - 3.46	0.019
Leukocytes > 50×10^9/L	0.79	2.22	1.26 - 3.89	0.006

**Logistic regression analysis. °Cox regression analysis. Poor risk cytogenetics according to Medical Research Council criteria.[21]*

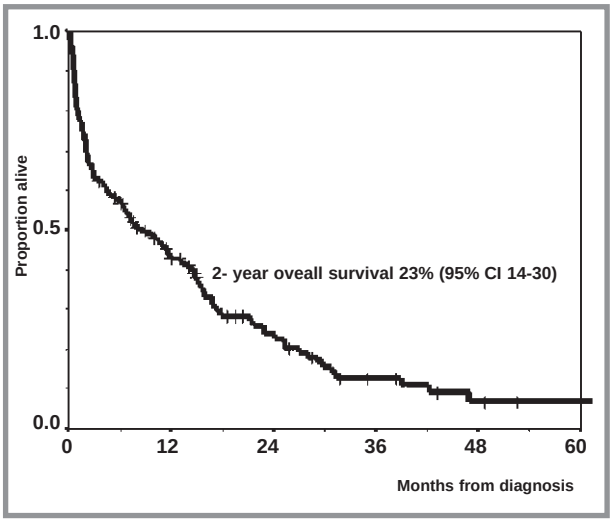

Figure 1. Estimated overall survival for patients intensively treated. Tickmarks indicate censored observations for patients last known to be alive.

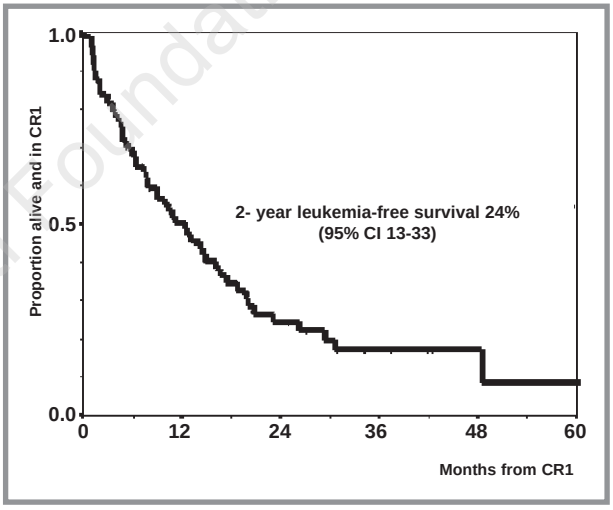

Figure 2. Estimated leukemia-free survival for patients intensively treated. Tickmarks indicate censored observations for patients last known to be alive and in first complete remission.

0.018) or leukocytosis (p= 0.03), and was poorer for patients with unfavorable cytogenetic than for those with favorable/intermediate risk with a borderline statistical significance (p=0.067). On multiple regression analysis of OS (Table 4), all 3 factors were found to have statistically significant independent prognostic effects. Thus, OS was significantly poorer in patients with unfavorable cytogenetics (p=0.035, compared with favorable/intermediate), age over 70 years (p=0.019, compared with age 60 to 70 years) or leukocytosis over 50×10^9/L (p=0.006, compared with lower white blood cell counts).

Leukemia-free survival

Of the 82 patients who achieved CR, 44 had relapsed and 12 had died in CR at the time of analysis (9 deaths related to consolidation aplasia, 2 related to ASCT and 1 due to infection not related to chemotherapy after ASCT). After a median follow-up of 13 months (range 5-60)for alive patients in first CR, the median LFS was 12 months (CI 8-17 months) and the estimated probability of 2-year LFS was 24% (CI 13-33%) (Figure 2). No factors significantly associated with LFS were identified on univariate analyses, with or without stratification for age. Of 9 patients who required 2 induction cycles to achieve CR, 7 relapsed from 2 to 20 months after induction and 1 died during consolidation treatment, none received an ASCT despite 5 being potential candidates, and only 1 is alive and in first CR after 42 months of follow-up. However, LFS for this subgroup of patients was not significantly shorter than that in patients entering remission with 1 cycle.

Effect of ASCT on leukemia-free survival

Of the 60 potential candidates for ASCT, 9 relapsed before a mobilization procedure had succeeded at a median of 108 days after the end of CI (range 32-160 days). For patients submitted to ASCT, the median LFS was 21 months (CI 10-32 months) and the estimated probability of 2-year LFS was 41% (CI 8-68%) while for candidate patients not submitted to ASCT, excluding those with early relapses, these values were 15 months (CI 11-18 months) and 24% (CI 9-39%), respectively. An exploratory landmark analysis was performed to compare the LFS of patients effectively submitted to ASCT (n=16) with that of the patients completing consolidation therapy and excluded from ASCT for reasons other than excessive toxicity of previous treatment or relapse before the mobilization procedure (n=35, patients' refusal 3, ASCT not indicated by attending physician 22 and inadequate mobilization 10). The patients submitted to ASCT and those excluded did not have statistically significant differences in age, initial performance status, AML subtype,

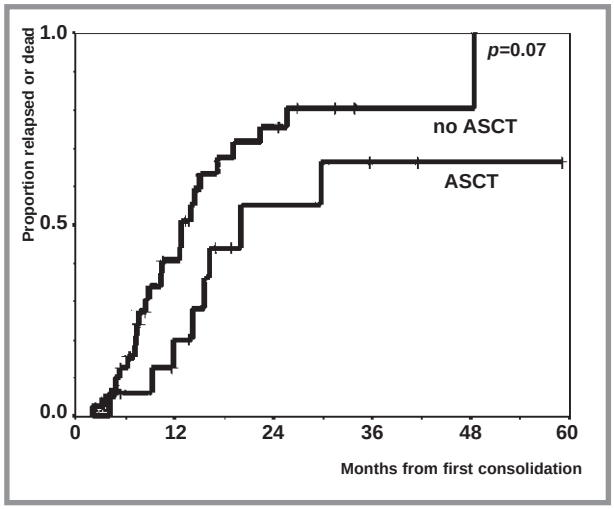

Figure 3. Landmark analysis of estimated time to relapse or death from first consolidation for 16 patients submitted to autologous stem cell transplantation (ASCT) and 35 patients receiving no further therapy. Tickmarks indicate censored observations for patients last known to be alive and in first complete remission. *p* refers to the log-rank test.

presence of trilineage dysplasia or cytogenetic risk group. For patients submitted to ASCT, the median time to relapse or death after the end of CI was 20 months (CI 10-30 months) and the estimated probability of 2-year LFS from that point was 39% (CI 6-71%), being 13 months (CI 11-15 months) and 22% (CI 6-39%), respectively, for candidate patients not submitted to ASCT. The LFS after C1 in patients submitted to ASCT was not statistically significantly prolonged (p=0.07) (Figure 3). The 10 patients with an insufficient stem cell harvest had a median time to relapse or death of 17 months (95%CI 2-33%) and thus represented the subgroup of non-transplanted patients who fared better after consolidation. In consequence, when these 10 patients were excluded from analysis, non-transplanted patients had a median time to relapse or death of 10 months (95%CI 5-16) and differences with patients submitted to ASCT became statistically significant (p=0.01).

Toxicities of chemotherapy and autologous stem cell transplantation

Most deaths related to toxicity during chemotherapy were due to infection (27 in induction, 9 in consolidation), hemorrhage (2 in induction, 1 in consolidation) or solid organ failure (heart 1, liver 3, lung 2). The overall rate of fatal toxicity was 24% during induction therapy and 10% during consolidation treatment. The median times to neutrophil recovery were 22 days (range 11-149) for induction and 17 days (range 6-44) for consolidation cycles. The median times to platelet recovery were 21 days (range 6-149) for induction and 19 days (range 7-66) for consolidation cycles. Other grades 3-4 chemotherapy-related toxicities are detailed in Table 5.

Table 5. Induction and consolidation toxicity (WHO grades 3-4) among the 135 intensively treated patients.

	ICE (N=148)	*MTZ-ARAC (N=75)*	*ASCT (N=16)*
Major hemorrhage	10 (2 deaths)	2 (1 death)	–
Infection	66 (27 deaths)	27 (6 deaths)	5 (3 deaths)
Gastrointestinal	17	3	14
Pulmonary	7 (1 death)	4 (1 death)	–
Neurological	3	1	–
Cutaneous	6	–	–
Hepatic	8 (2 deaths)	2 (1 death)	1
Renal	3	1	–
Cardiac	3 (1 death)	1	–
Days to platelets > 20×10^9/L	21 (6 – 149)	19 (7 – 66)	25 (12 – 65)
Days to neutrophils >0.5×10^9/L	22 (11 – 149)	17 (6 – 44)	16 (9 – 35)

ICE: idarubicin, cytarabine, etoposide; MTZ: mitoxantrone; ARAC: cytarabine; ASCT: autologous stem-cell transplantation.

Transplant-related mortality (TRM) occurred in 3 patients (19% of patients receiving ASCT). The causes of TRM were infections either in the setting of prolonged pancytopenia (n=2) or after hematological recovery (n=1). One case of non-fatal veno-occlusive disease was recorded. The estimated median time to hematologic recovery was 16 days for neutrophils (range 9-35) and 25 days for platelets (range 12-65). The median time to hospital discharge after day 0 of the transplant was 18 days (range 10-40). Other grade 3 or 4 transplant-related toxicities are reported in Table 5.

Discussion

The treatment of elderly patients with AML is still a matter of debate.[11,22,23] While there is concern about the unfavorable impact of intensive therapy on the quality of life,[24,25] it is clear that a very significant proportion of patients benefit from this approach.[9,26] The results of treatment in these patients are also controversial. Epidemiological data suggest that survival has not

improved in recent years,[27] while comparison of clinical studies suggests that better supportive measures have diminished induction-related mortality and, therefore, CR rates have risen.[11] Even if CR is short-lived, achievement of CR seems to offer the best chances for both prolonged survival and better quality of life.

In the present study, the participating centers registered all cases of AML in patients 60 years or older in order to assess the proportion of patients considered fit for treatment with current supportive measures. The induction protocol could be applied in about a half of all the patients diagnosed. However, while only 32% of the patients over 70 received intensive treatment, 76% of patients from 60 to 70 years underwent this treatment. Only 3 patients refused intensive treatment when confronted with the diagnosis of AML. Thus, despite the expected high early mortality, not only were most patients aged 60 to 70 years considered fit enough to receive intensive treatment but also most patients in this age group did not accept to receive only palliative care. The data from the 119 patients who received palliative or non-intensive treatment, who had a median survival of 2 months, may argue in favor of assuming the risk of an intensive approach. A previous protocol of the CETLAM group,[28] recruited 90 patients over 60 years (13 over 70 years) in a 7-years period (1989-1997). Although that study did not include a registry of untreated patients, it is likely that the proportion of patients treated aggressively has increased in recent years. The same group recruited 159 patients under 51 years in a shorter period (1989-1994) for a parallel protocol including ASCT or allogeneic stem cell transplant.[29]

We chose a conventional intensive chemotherapy approach to allow the comparison of early mortality and CR rate with similar studies since to date, novel drugs[30-32] or combinations[33-38] have not proven to be superior to cytarabine-anthracycline induction treatments. The induction death rate was 24%, similar to that in previous reports[4,33,39] and not much higher than that for protocols including low-dose daunorubicin[26] or mitoxantrone.[40,41] Most deaths were related to major infections, thus early death rates may potentially be improved with current and future supportive measures, particularly antifungal drugs. A wider inclusion of elderly patients in intensive protocols may obscure improvements in CR rates, and, in fact, selection bias may account, in part, for the stable rates of early deaths in studies in the last two decades[11] despite obvious advances in supportive care. Advanced age reduced the feasibility of intensive induction treatment but also reduced the chance of surviving it in patients considered fit enough to receive the induction treatment. Unfavorable cytogenetics was a significant and independent prognostic factor associated with a low CR rate. Age and poor risk cytogenetics were the only factors associated with failure to achieve CR both in univariate and multivariate analyses. Multidrug resistant phenotype[12] was not analyzed systematically. Other reported prognostic factors, such as immunophenotype[40,42] and trilineage dysplasia, were not found to be significantly associated with CR.

Infection remained the main cause of death and the main cause of exclusion from further treatment after consolidation with mitoxantrone and cytarabine. Overall, 60 patients, 23% of all the patients diagnosed and 44% of patients receiving intensive treatment, were in an adequate condition to proceed to further consolidation treatment. Among patients 70 years or older, 9 (36% of those receiving intensive treatment) completed induction and consolidation chemotherapy successfully.

In patients up to 55 years, the addition of myeloablative chemotherapy plus TBI and ASCT has improved LFS in some studies when compared with no further treatment after induction and consolidation treatment.[43] In elderly patients with a good performance status, ASCT does not seem to be particularly toxic although studies specifically addressing this question are limited.[44] Thus, we explored the feasibility of performing ASCT after aggressive induction and consolidation therapy in our cohort of elderly patients. Both early relapse (15%) and insufficient mobilization of stem-cells (17%) were, as expected, major causes of failure to perform ASCT. In the study design, patients with a poor performance status or major toxicity after consolidation were excluded from ASCT; conversely all patients having an adequate recovery after consolidation were automatically considered candidates for ASCT. As the physical condition of patients in first CR was not expected to deteriorate while waiting for ASCT, the proportion of potential candidates withdrawn because of medical conditions was unexpectedly high (27%). Although a proportion of patients might have been found unfit during pre-transplant evaluations, other unexpected factors played a role in the low recruitment for ASCT. Age may have been a factor causing withdrawal of patients from ASCT programs in our series (6 out of 9 candidate patients older than 69 were withdrawn). However, statistically significant differences in ASCT indications were found between centers having transplant units and those without them. This factor is obviously undetected in single center studies and may have been undetected or not reported in collaborative protocols. However, the availability of a transplant unit may be very relevant in clinical practice. The specific structure of the CETLAM group, which includes hospitals with hematology services of different levels of complexity, led to the detection of this unexpected factor. While geographical distance may be a minor question when a younger patient is a

candidate for an autologous or allogeneic transplant, this problem may not be irrelevant when referring patients with advanced age. In most cases transfer of such patients also implies transfer of one or more relatives or care-givers. The final decision may often lay with these care-givers. Moreover, the benefit of ASCT in the elderly is not clearly established. However, it is noteworthy that in our study only 3 patients (2 of them older than 70) refused to be submitted to ASCT when it was offered.

Less than a half of the patients with AML who were > 60 years old completed the first consolidation cycle with an adequate performance status to be submitted to ASCT and most of these patients have short LFS and OS whatever their subsequent treatment; thus, the feasibility of a randomized study comparing ASCT with other consolidation strategies or with no further treatment may be limited. Moreover, AML is a heterogeneous disease including groups with particularly poor prognosis[45,46] making comparisons even more complex. However, even if there is not a definitively proven benefit of ASCT, the option of no further treatment may be difficult to offer to patients with an adequate performance status and intermediate or low risk cytogenetics, whatever their age. In this study, our rationale for comparing patients submitted to ASCT with patients in whom treatment was not continued was based on the assumption that a relevant proportion of patients may not have been offered an ASCT because of reasons other than obvious unfitness. Patients reported as unfit after consolidation and patients relapsing in the first three months after consolidation (before a potential ASCT may have been performed) were excluded from the landmark analysis. Patients submitted to ASCT were compared with patients refusing ASCT, those unable to mobilize sufficient stem-cells and those not proposed for an ASCT by their attending physician despite not being reported as having a bad general status after consolidation. The difference in the results of the two groups should be evaluated with caution considering the possible impact of likely differences in performance status and the fact that the study was not prospectively designed to address this comparison. The reason for the relatively better outcome of patients with an insufficient stem-cell harvest as compared with other patients not receiving ASCT is unclear. Similar intensities of cytostatic damage to normal stem-cells and their leukemic counterparts may explain the effect in part, but such a conclusion cannot be derived from our observations and consequently the exclusion of these patients from the landmark analysis *a posteriori* is not justified. However, even if the tendency to a possibly inferior outcome without ASCT should be considered only suggestive, the results certainly do not warrant one consolidation cycle only over one consolidation cycle followed by ASCT. Moreover, hematologic and extrahematologic toxicity of the ASCT procedure was acceptable and very similar to that reported for younger patients,[43,47] thus rendering ASCT as an adequate alternative to high-dose cytarabine or other consolidation strategies. Given the significant toxicity and even mortality associated with consolidation treatments in elderly patients the administration of multiple consolidation cycles does not appear to be an adequate strategy.[3] Tolerance to high-dose cytarabine is low in patients of advanced age[4] and conventional allogeneic-SCT is hardly ever feasible. Non-myeloablative allogeneic-SCT is a promising option for elderly patients although its efficacy remains to be established.[48-50] Thus, while the value of the more recent strategies is under validation, ASCT appears to be a reasonable consolidation treatment for patients in first CR. The still high relapse rate after ASCT remains a crucial and yet unsolved issue. An independent and statistically significant association was found among advanced age, poor risk karyotype and a high white blood cell count and OS. Although the statistical power was reduced by the low number of patients with unfavorable features achieving CR, we were not able to demonstrate a significant association between these factors and LFS. However, it is noteworthy that a recent phase III SWOG trial[12] including 211 patients, found identical prognostic factors for OS and LFS, thus the possibility of achieving good quality remissions in a small minority of poor risk patients should not be excluded.

In conclusion, at least a quarter of elderly patients up to 70 years old with *de novo* AML benefit from standard intensive treatment. The proportion of patients considered fit for treatment and the benefit of an intensive approach may increase with time due to improved supportive measures. In this subgroup of patients, ASCT is feasible, has a tolerable toxicity and may have a positive impact on leukemia-free survival.

JMR, JS and SB were primarily responsible for the design of the study protocol. AO and JMR wrote the paper. The remaining authors, who qualified for authorship according to the WAME criteria, were specifically responsible for the following parts of the content: AO and JMR for data handling and statistical analyses. JE and SB revised the manuscript. AO, JMR, JE, RG, SB, JB, CP, AL, MT, JB, JMS, PV, EC, AV, AJ, MB, JS, EM and EF performed the studies at diagnosis and the clinical follow-up of the patients.

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