Acute Myeloid Leukemia • Research Paper

Treatment of primary acute myeloid leukemia: results of a prospective multicenter trial including high-dose cytarabine or stem cell transplantation as post-remission strategy

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A B S T R A C T

Background and Objectives. To evaluate a regimen of induction and consolidation chemotherapy, followed by a post-remission therapy which depended on age and cytogenetics, in patients with primary acute myeloid leukemia.

Design and Methods. Two hundred patients up to 60 years old received idarubicin, standard dose cytarabine and etoposide as induction chemotherapy and one consolidation course including intermediate dose cytarabine and mitoxantrone. Subsequently, patients with favorable cytogenetics, [i.e., t(8;21), inv(16)] were scheduled to receive 2 courses of high-dose cytarabine. The remainder were scheduled for allogeneic stem cell transplantation (SCT), if ≤ 50 years old and with an HLA-identical sibling, or autologous SCT if >50 years old or lacking a donor.

Results. In patients with favorable cytogenetics the 4-year probabilities of survival and leukemia-free survival (LFS) were 62±9% and 41±10%, respectively. The results were better in patients with t(8;21). LFS at 4 years in patients ≤ 50 years old allocated to allogeneic SCT was 41±9% vs 48±8% after autologous SCT (p=0.22). Patients >50 years old assigned to auto-SCT had a 4-year LFS of 17±9%. Adverse cytogenetics and white blood cell count ≥ 20×10^9/L at diagnosis were associated with lower probability of survival and leukemia-free survival.

Interpretation and Conclusions. We confirmed that high-dose cytarabine seems a good option for patients with t(8;21). Autologous and allogeneic SCT led to similar leukemia-free survival in patients ≤ 50 years of age. In older patients, the results of auto-SCT were poor. Finally, cytogenetics and white cell count at diagnosis, together with new prognostic markers, should be considered in the design of future risk-adapted trials.

Keywords: acute myeloid leukemia, high-dose cytarabine, stem cell transplantation.

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The overall rate of complete remissions (CR) in adults with primary acute myeloid leukemia (AML) is 65-80%.[1-4] For many years daunorubicin has been the most widely used anthracycline for induction chemotherapy. One study suggested that better remission rates may be obtained in younger patients with idarubicin,[5] although data from updated trials failed to demonstrate any advantage.[6,7] The need for intensive post-remission therapy in AML is well established,[8,9] since most patients in CR subsequently relapse. Among the various post-remission strategies, allogeneic stem cell transplantation (allo-SCT) has the maximal antileukemic effect but is associated with a relatively high procedure-related mortality.[10] Several randomized[11,12] and non-randomized[2,13-16] studies have reported a better LFS after auto-SCT than after post-remission chemotherapy. Conversely, other studies in adults have failed to confirm this advantage from auto-SCT.[3,16] High-dose cytarabine (HDAC) seems the best CT option, particularly in patients with favorable cytogenetics, such as t(8;21) (q22;q22) or inv(16), who usually experience prolonged failure-free survival after this treatment.[17,18] This supports the concept that the impact of the different post-remission therapies may vary according to the patients' cytogenetic group risk.[18-22] However, there are no randomized studies investigating what is the best therapeutic approach in each prognostic category.

We present the results of a prospective multicenter trial in adult patients with primary AML. The induction chemotherapy, including idarubicin, cytarabine and etoposide, was aimed at optimizing the quality of CR, avoiding early relapses and making post-remission treatment feasible. With the

intention to control toxicity which could compromise the treatment plan, as occurred in our previous protocol,[2] a single consolidation course without HDAC was given. Subsequently, and as a key objective of the study, we investigated the results of stratifying the treatment on the basis of the patient's age, cytogenetics, and availability of an HLA-identical sibling.

Design and Methods

Patients

From May 1994 to January 1999, 200 consecutive patients with primary AML were included in this study at the adult Hematology Departments of 11 hospitals in Catalonia and the Balearic Islands (Spain). Inclusion criteria were as follows: (i) age up to 60 years, (ii) diagnosis of AML (acute promyelocytic leukemia excluded) according to the FAB classification, (iii) no history of myelodysplasia or previous cytotoxic drugs or radiation, and (iv) absence of severe concomitant disease. The main characteristics of the patients are listed in Table 1. Cytogenetics was categorized as in the MRC AML 10 trial.[21]

Table 1. Characteristics of the patients at diagnosis.

No. of patients	*200*
Sex (male/female)	99 (49)/101 (51)
Age	
Mean age±SD (years)	41+12
Median age	42
Range	16-60
Adults ≤50 years	140 (70)
Adults > 50 years	60 (30)
FAB subtype	
M0	12 (6)
M1	33 (17)
M2	44 (22)
M4	59 (29)
M5	44 (22)
M6	7 (3)
Unclassified	1 (1)
Cytogenetics	165/200 (82%)
Favorable	29 (17)
t(8;21)	13
inv(16)/t(16;16)	16
Intermediate*	117 (71)
Adverse°	19 (12)

**Intermediate: no abnormalities, +8, 11q23, +21, del(7q), del(+9), other numerical, other structural; °Adverse: complex, -7, abn(3q), del(5q), -5. Percentages in parentheses*

Treatment plan

Induction chemotherapy

The induction chemotherapy was the ICE regimen, consisting of idarubicin 10 mg/m^2 intravenously (IV) over 30 minutes on days 1,3 and 5; cytarabine 100 mg/m^2 IV in a continous infusion on days 1-10 (n=68), or on days 1-7 (n=132); etoposide 100 mg/m^2 IV in a 1-hour infusion on days 1-5 (n=68), or on days 1-3 (n=132). The modification in the total dose of cytarabine and etoposide was made to decrease significant gastrointestinal toxicity after an interim analysis. Patients not in CR after one course of treatment, with a decrease > 25% in bone marrow blasts, received a second course of ICE.

Consolidation chemotherapy

Patients received a single course of intermediate dose cytarabine 500 mg/m^2 in a 2-hour IV infusion, every 12 hours IV days 1-6, and mitoxantrone 12 mg/m^2 in a 15-minute IV infusion on days 4-6.

Intensification

Patients with t(8;21) or inv(16) were scheduled to receive two courses of HDAC 3g/m^2, administered by a 2-hour infusion every 12 hours on days 1, 3 and 5. The remaining patients were treated as follows: (i) patients aged ≤ 50 years with an HLA identical sibling received an allo-SCT, and (ii) patients aged >50 years or without an HLA-identical sibling were treated with an auto-SCT. The characteristics of the patients according to their intended treatment are listed in Table 2.

HLA-typing

HLA-typing of patients in CR (≤ 50 years old without favorable cytogenetics) and their siblings was performed either after induction or after intensification therapy.

Stem cell collection

Bone marrow (BM) (n=23) or peripheral blood (PB) (n=23) cells in more recent cases were collected and cryopreserved (in auto-SCT) after hematologic recovery from consolidation therapy, following standard methods. Most of these procedures were performed in the reference centers where the patients finally received their auto-SCT. The dose of granulocyte colony-stimulating factor to mobilize PB cells was 10 μg per kilogram of body weight daily for five days. The minimum CD34$^+$ target dose was 2×10^6/kg both in auto and allo-SCT. However, 1 patient ≤ 50 years old was autografted with 0.9×10^6/kg CD34$^+$ cells. Non-manipulated products were administered in autografts, whereas T-cell depletion according to previously described methods was performed in 3 of 4 allogeneic bone marrow[23,24] and in 18 of 24 PB stem cell transplants. CD34$^+$ selection was performed in the latter cases.[25] The goal was to infuse a CD3$^+$ cell dose of 0.3×10^6/kg. The median numbers of CD34$^+$ cells and CD3$^+$ cells infused into the patients were 4.1×10^6/kg (range; 0.7 –13.4) and 0.3×10^6/kg (range, 0.05-1.0), respectively.

Table 2. Characteristics and results according to the intention to treat (patients in CR).

Characteristic	*Allo-SCT (n=33)*	*Auto-SCT ≤ 50 years-old (n=49)*	*Auto-SCT >50 years-old (n=37)*	*High Dose Cytarabine (n=24)*	*p*
Age					
Mean age ± SD (years)	36±9	35±11	55±3	39±11	NS[1]
Median age	37	37	55	38	
Range	16-50	16-50	51-60	16-58	
Sex (male/female)	14/19	29/20	12/25	11/13	0.09
Leukocytes ($\times 10^9$/L)					
Median	26	23	16	14	0.544
Range	2-186	1-270	1-115	1-156	
Transplant-related mortality % ± SE	23±9	3±3	23±6	14±7	0.02 0.005[1]
4-year probability:					0.24
Overall survival % ± SE	41±9	52±8	38±8	61±6	0.22[1]
Censored/Total	14/33	27/49	14/37	11/29	0.10[2] 0.17[3]
Leukemia-free survival % ± SE	42±8	48±8	17±9	41±10	0.2
Censored/Total	14/33	25/49	10/37	14/24	0.44[1] 0.03[2] 0.0004[3]

[1]Allo-SCT vs auto-SCT < 50 years-old; SCT: stem cell transplantation; [2]Auto-SCT < 50 years old vs >50 years old; [3]t(8;21) vs inv(16); SD: standard deviation; SE: standard error.

Conditioning for SCT

The conditioning regimen for transplantation consisted of cyclophosphamide 120 mg/kg IV on 2 consecutive days and fractionated total-body irradiation (12 to 14 Gy in three to seven fractions) in 72 of 84 transplants (86%) (46 of 56 auto-SCT and 26 of 28 allo-SCT). The remaining 12 patients (10 auto-SCT and 2 allo-SCT) received busulfan 16 mg/kg orally plus cyclophosphamide 120 mg/kg IV.

Other measures

Graft-versus-host disease (GVHD) prophylaxis was as follows: 14 (50%) patients received cyclosporine plus prednisone, 4 (14%) cyclosporine plus 4 doses of methotrexate,[2] 7 (25%) cyclosporine plus 3 doses of methotrexate,[25] and 3 (11%) cyclosporine alone.

Patients with acute and/or chronic GVHD were diagnosed and managed according to previously described methods.[26,27] Antimicrobial agents to prevent bacterial, fungal and viral infections were administered following the usual policies at each center. Patients received granulocyte colony-stimulating factor only in case of engraftment failure and severe infection. All blood products were irradiated with a minimum of 20 Gy.

Response criteria

Complete and partial remissions and relapse were defined according to standard criteria.[28] Patients with less than a 25% reduction in marrow leukemia cells after the first course, and those who did not achieve either a complete or partial remission after two courses, were considered as refractory and withdrawn from the study.

Statistical analysis

Descriptive statistical analysis of the main characteristics of the patients was performed. Differences between groups were measured by Fisher's exact test or the Kruskal-Wallis test. Survival probabilities were estimated using the Kaplan-Meier method.[29] Survival curves were compared by the log-rank test[30] and the Cox proportional hazards model was used to estimate the risk ratio of events after controlling for prognostic variables.[31] Standard definitions for reporting results of bone marrow transplants were used.[30] The possible influence of several characteristics on overall survival (OS), leukemia-free survival, duration of CR and outcome of SCT or HDAC intensification was studied. Univariate analysis of prognostic factors included the following variables: age, sex, leukocyte count at diagnosis, FAB subtype, number of induction courses, dose of induction (10 vs 7 days), time to obtain the CR (days), availability of a HLA-identical sibling, interval between achieving CR and undergoing SCT, cytogenetic group (favorable, intermediate vs adverse), type of conditioning regimen (chemotherapy vs chemotherapy plus TBI), purging of stem cells and source of SCT. Statistical studies

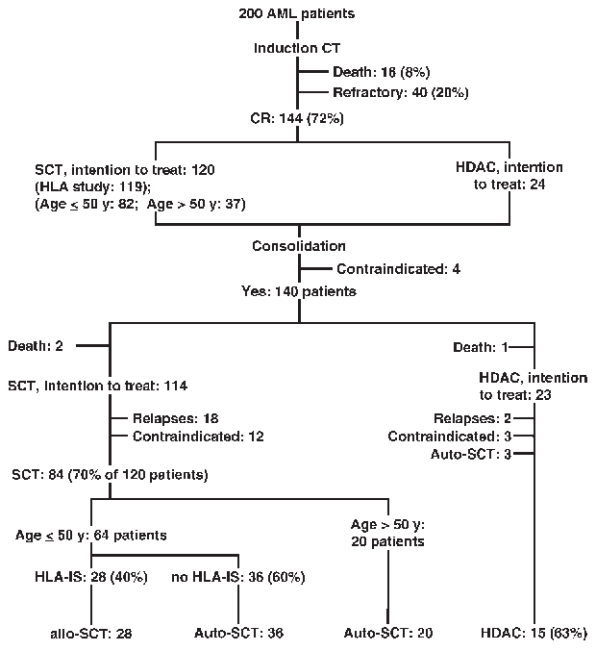

Figure 1. Feasibility and results of the treatment schedule. SCT: stem cell transplantation; HDAC: high-dose cytarabine; HLA-IS: HLA-identical sibling.

were performed using of the SPSS 9.0 statistical package (1999; SPSS, Chicago IL, USA).

Results

The main results of the treatment plan in the 200 patients are summarized in Figure 1.

Results of induction chemotherapy

One patient died on day 2 of treatment. CR was obtained in 144 of the 200 patients (72% of the series). No significant differences in CR rates were found between patients treated with the 10-day vs 7-day induction therapy protocol: 51 of 68 (75%) patients who received 10 days of cytarabine achieved CR as did 94 of 132 (71%) treated for 7 days (p=0.6). The main reason for moving from the original 3+5+10 schema to the 3+3+7 regimen was grade 3-4 gastrointestinal toxicity after the 3+5+10 regimen, particularly liver toxicity, which developed in 28% of patients and delayed the following course of chemotherapy. When the two regimens were compared, gastrointestinal toxicity was higher after the 3+5+10 induction regimen (28% vs 10%, p=0.01). In contrast, no significant differences between recipients of the two dose regimens were observed regarding infectious complications (35% vs 37%), relapse rate (53% vs 58%), death during induction (9% vs 8%), proportion of patients allocated to transplant (60% vs 60%) and finally receiving the procedure (48% vs 42%). Age did not affect the CR rate, the number of courses necessary to achieve remission, or the mortality during induction. Forty-one of 60 patients (68%) older than 50 years and 103 of 140 younger patients (74%) attained CR (p=0.4). Among patients who achieved CR, 117 (81%) had received a single induction course, whereas 27 (19%) patients required 2 courses. The frequency of deaths related to induction therapy was 8% (16 patients). The main causes of death were pulmonary infection (12 cases), enterocolitis (2 cases), and septic shock (2 cases). Forty patients (20%) were considered as refractory, 22 after one course of induction CT and 18 after 2 courses. Thirty of these 40 patients (75%) received salvage chemotherapy and, finally, 15 patients (37%) underwent SCT in second CR (7 auto-SCT and 8 allo-SCT, 2 of which haploidentical). Five out 40 patients (12%) were alive and in complete remission after a median follow-up of 31 months (2-62). Among the 164 patients (82%) for whom results of cytogenetics at diagnosis were available, the CR rate in patients with an adverse karyotype was 15% as compared to 74% in the other groups (p<0.0001).

Consolidation

Four patients in CR did not receive consolidation therapy because of hepatitis C virus infection (n=1), hepatic candidiasis (n=1) or intense cytopenias (n=2) (Figure 1). Three of 140 patients (2%) who received the consolidation therapy died of bacterial infection; one of them was in the HDAC group with inv(16) and the other 2 were scheduled to receive SCT.

HDAC treatment

After completion of consolidation therapy, 24 patients with t(8;21) and inv(16) in CR were allocated to receive 2 HDAC courses. The main characteristics and outcomes are listed in Table 2. Of note, the median white blood cell (WBC) count at diagnosis was significantly higher in patients with inv(16), being 52 (range 1-156)$\times10^9$/L, than in those with t(8;21), in whom it was 12 (range 3-35)$\times10^9$/L (p=0.006). Fifteen of these 23 patients (65%) finally received HDAC (Figure 1). The main results in the group of 23 patients are shown in Table 2. Remarkably, the 4-year probability of LFS was significantly better in patients with t(8;21), being 81 + 11%, than in those with inv(16) in whom it was 8 + 7%, (p<0.0001), due to a higher relapse rate in the latter group.

Stem cell transplantation

The overall feasibility of the post-remission treatment is shown in Figure 1. Eighty-four of the 120

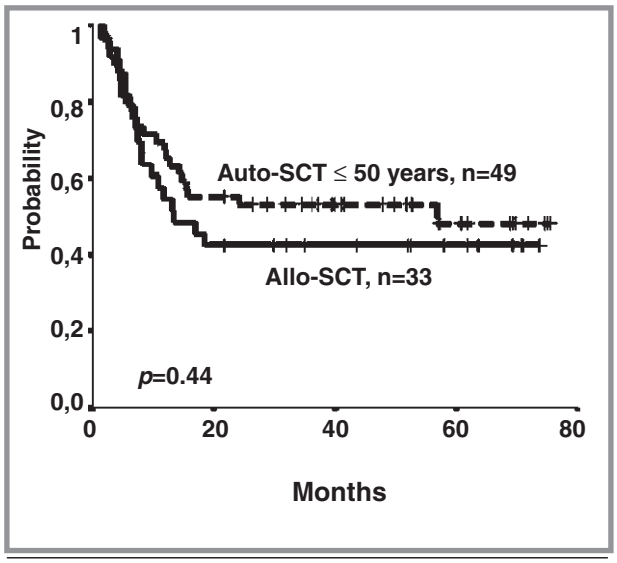

Figure 2. Leukemia-free survival since CR according the intention to treat (autologous or allogeneic transplantation) in patients ≤ 50 years old.

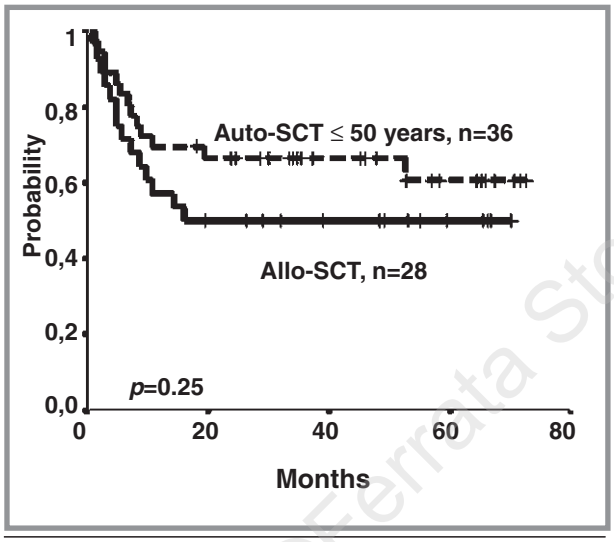

Figure 3. Leukemia-free survival after transplantation in patients ≤ 50 years old.

Table 3. Characteristics and results in transplanted patients.

Characteristic	*Allo-SCT (n=28)*	*Auto-SCT ≤50 years-old (n=36)*	*Auto-SCT >50 years-old (n=20)*	*p*
Age				
Mean age + SD (years)	35±10	34±10	55±3	NS[1]
Median age	36	36	55	
Range	16-50	15-48	51-60	
Sex (male/female)	14/14	21/15	9/11	0.6
Leukocytes (×10⁹/L)				
Median	25	18	26	0.5
Range	2-186	1-128	2-115	
Conditioning				
CT	2	5	5	0.2
CT + TBI	26	31	15	
Source Stem Cells				
Bone Marrow	4[2]	14	9	0.04[1]
Peripheral Blood	24[2]	22	11	
TRM at 100 days % ±SE	18±7	3±3	15±10	0.05
4-year probability				
Overall survival % ±SE	48±10	60±10	48±12	0.43
Censored/Total	14/28	23/36	10/20	
Leukemia-free survival %±SE	50±9	60±9	15±12	0.17
Censored/Total	14/28	23/36	7/20	0.25[1] 0.04[3]
Source of Stem Cells				
PB (%±SE) (n)	50±10(24)	64±10(22)	51±16(11)	0.70
BM	50±25(4)	63±13(14)	11±10(9)	0.64[4] 0.35

[1]Allo-SCT vs auto-SCT < 50 years-old; [2]T-cell depletion of 3 BM and 18 PB; [3]Auto-SCT < 50 years-old vs auto-SCT >50 years-old); [4]Auto-SCT < 50 years-old using BM vs PB; [5]Auto-SCT >50 years-old using BM vs PB; TRM: transplant-related Mortality; PB: peripheral Blood; BM: bone marrow.

patients intended to have a SCT actually received this procedure (70%). The main characteristics and results, divided according to the intended treatment, are shown in Table 2.

Patients ≤50 years old

Eighty-two patients ≤ 50 years old in CR were HLA-typed and 33 of them (40%) had an HLA-identical sibling (Table 2). Allo-SCT was performed in 28 (85%) of these patients (Table 3). The reasons for the remaining 5 patients not being transplanted were relapse in 3 patients, refusal in 1 and toxic death during consolidation in 1. Forty-nine patients ≤ 50 years old were eligible for auto-SCT. Auto-SCT was performed in 36 patients (65%) (Table 3), whereas 9 were not transplanted due to early relapse, 1 refused the procedure, 1 had hepatotoxicity, 1 suffered from another toxicity and 1 had had a poor harvest.

The main results according to intention to treat are shown in Table 2. No significant difference in LFS or relapse rate was observed between patients submitted to allo-SCT and those who received auto-SCT (Table 2 and Figure 2). In contrast, transplant-related (TRM) was higher in the allo-SCT group (23 + 9% vs 3 + 3%, p=0.005). A median of 3.7 months after achieving CR, 64 patients ≤ 50 years old were transplanted. Twenty-eight patients received an allo-SCT at a median of 3.5 (2.3-6.9) months after CR achievement. The main

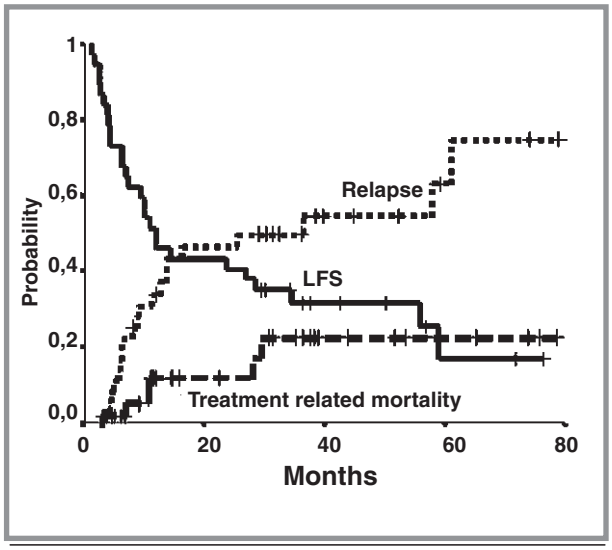

Figure 4. Leukemia-free survival since CR, relapse and TRM in patients > 50 years old according to the intention to treat with autologous transplantation (n=37).

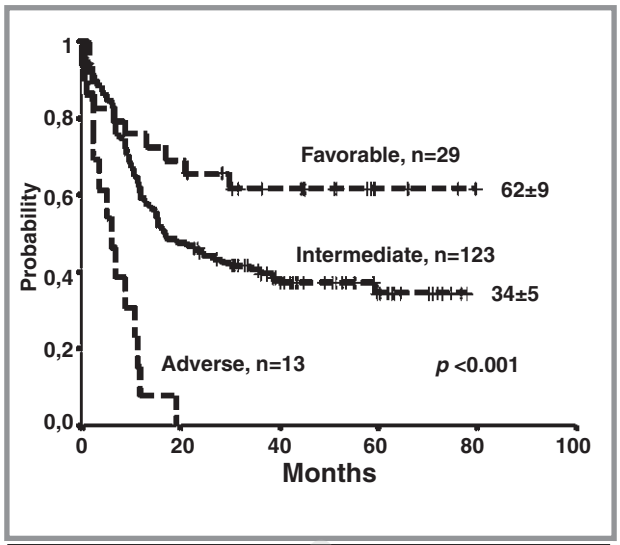

Figure 5. Overall survival according to cytogenetics at diagnosis.

characteristics and results of this group are listed in Table 3 and shown in Figure 3. No engraftment failure was observed. The probability of developing grades II-IV acute GVHD was 28 + 8% at 100 days. Six of 23 patients at risk of chronic GVHD developed this complication with a 3-year probability of 28 + 9%. One BM and 8 PB allo-SCT recipients (6 T-cell depleted, 3 non-T-cell depleted) relapsed after a median follow-up time of 8 (range 4-16) months and all of them subsequently died. TRM occurred in 4 T-cell-depleted and 1 T-cell replete SCT. The cause of death was infection in 3 patients (2 bacterial and 1 fungal), multiorgan failure in 1 and acute GVHD in 1.

Thirty-six patients ≤ 50 years-old received an auto-SCT at a median time of 3.7 (2.4-8.5) months after achieving CR. The main characteristics and results of the autografted patients are listed in Table 3 and shown in Figure 3. The median time to granulocyte recovery was 21 days. Platelet recovery was achieved after a median of 39 days. Four patients showed a slow granulocyte recovery and three of them received G-CSF. One patient died of infection secondary to graft failure.

Patients >50 years old

Of the 37 patients eligible for auto-SCT in this age group, the procedure was performed in 20 (54%). Six patients were not transplanted because of early relapse, 5 refused the procedure, 2 had hepatotoxicity, 1 suffered from another toxicity, 1 had a poor harvest, one had chronic candidiasis and 1 patient died during consolidation therapy. The main results according to the intention to treat are shown in Table 2 and Figure 4. The 4-year probability of LFS was 17 + 9% which was significantly lower than in patients ≤ 50 years old who received an auto-SCT (p=0.03). The median follow-up of the alive patients was 44 months.

Twenty patients >50 years old received an auto-SCT at a median time of 115 days after achieving CR. The main characteristics and results of the autografted patients are listed in Table 3. Five patients experienced slow granulocyte recovery and 3 of them required G-CSF. Four of these patients died, 2 of infection, 1 of graft failure and 1 of disease progression without recovery.

The median follow-up of the 7 patients alive without evidence of relapse was 39 months. LFS was significantly poorer in patients >50 years old than in younger patients receiving auto-SCT (p=0.04) (Table 3). The causes of TRM were graft failure in one case, septic shock and fungal infection 2 years post-transplant in 2 patients, multiorgan failure in 1 and pulmonary hemorrhage in 1. Of note, 2 of the 8 relapses occurred 53 and 49 months after auto-SCT. In 1 of these patients a pathological clone suggesting a secondary myelodysplastic syndrome was evident in cytogenetic studies. Both patients experiencing a late relapse received conventional chemotherapy and remain alive 15 and 8 months after treatment. No significant differences in LFS and relapse incidence were found when comparing BM and PB as the source of the progenitor cells p=0.3 and p=0.8, respectively. In contrast TRM was significantly lower when PB was used 12% vs 50% (p=0.05).

Prognostic factors

Parameters that were found to be significantly associated with a shorter LFS in multivariate analysis were adverse cytogenetics (RR of treatment failure: 19, 95%

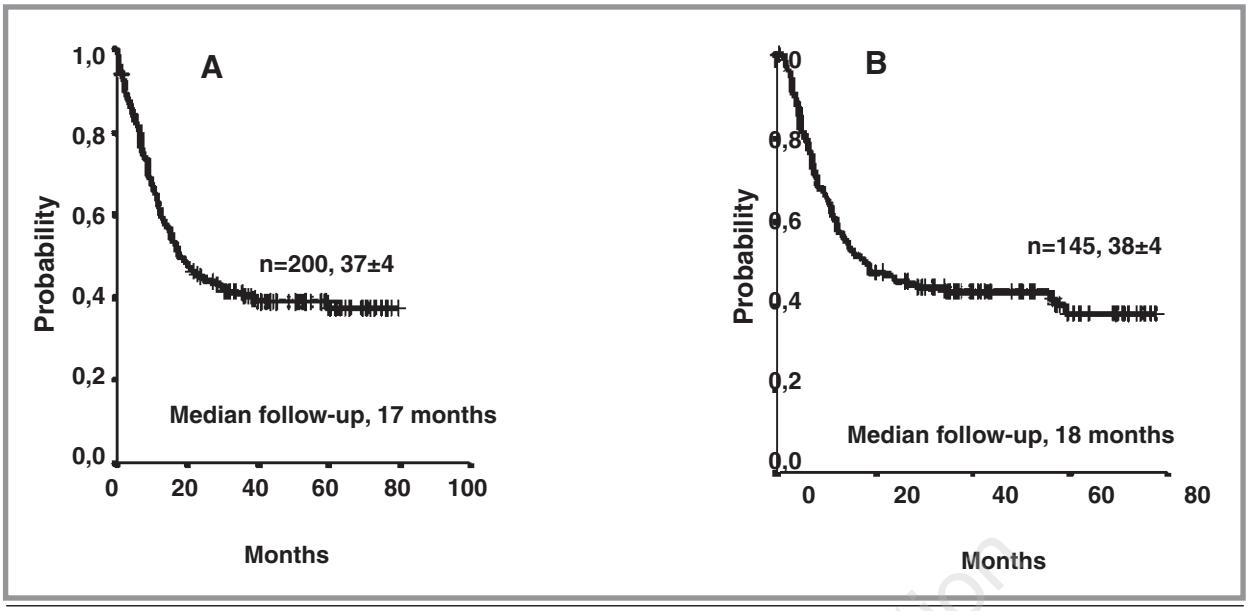

Figure 6. A. Overall survival of whole series; B. Leukemia-free survival since CR of whole series.

CI 3.3-114, p=0.001) and WBC count at diagnosis >20×10^9/L, (RR: 3.4, 95% CI 1.7-6.7, p<0.001). Cytogenetic group (RR: 32, 95% CI 4.9-218.7, p=0.004) and WBC count at diagnosis (RR: 3.8, 95%CI 1.8-8.0, p=0.001) also adversely influenced OS (Figure 5). Parameters that were found to be highly significantly associated with increased relapse rate were female sex (RR: 2.1, 95% CI 1.1-3.9, p=0.02), WBC count at diagnosis >20×10^9/L (RR: 3.4, 95%CI 1.6-7.2, p=0.001) and adverse cytogenetics (RR: 10.1, 95% CI 1.0-101.1, p =0.04). Furthermore, adverse cytogenetics (RR: 38.1 CI 95% 3.0-477, p=0.005) and WBC count >20×10^9/L (RR: 6.01 CI 95% 1.4-24.4, p=0.01) were found to be significantly associated with early relapse (within the first 3.5 months after achieving CR).

Prognostic factors associated with worse LFS after

Table 4 . Outcome of non-transplanted patients (n=36).

		Intention To Treat		
Characteristics	*Median Age*	*Allo-SCT*	*Auto SCT*	*Outcome*
Intensification contraindicated (n=4)	(range) 53 (51-60)		4	1 alive in 1st in CCR with no treatment and OS of 77 months; 3 died of progression, 1 after palliative treatment
Death in consolidation (n=2)	50 (44-57)	1	1	2 died of infection
Contraindication (n=12)	50 (44-56)			5 died of progression, 4 after CT reinduction; 7 alive (4 in 1st CCR and no further CT and 1 with HDAC consolidation; 2 in 2nd CR after CT reinduction) with a median OS of 47 (36-70) months
Refusal		1	6	
Toxicity			3	
Poor harvest			2	
Relapse pre-SCT (n=18)	53 (19-60)	3	15	17 died of progression, 13 after CT reinduction; 1 alive in 2nd CCR with an OS of 44 months

CCR: continuous complete remission; OS: overall survival; SCT; stem cell transplant; CT: chemotherapy; HDAC: high dose cytarabine.

allo-SCT were age >30 years, (RR 9.7, CI 95% 1.2-78.6, p=0.03); female sex (RR 7.6, CI 95% 1.2-46.7, p=0.02); the time between CR and allo-SCT being above the median of 3.5 months (RR 2.1, CI 95% 1.06-4.4, p=0.03); and the presence of grade II-IV acute GVHD (RR 13.1, CI 95% 0.9-178.02, p=0.05). For patients who received an auto-SCT, a WBC count >20×10^9/L at diagnosis (RR 2.56, CI 95% 1.06-6.2, p=0.03) and the time between achieving CR and receiving the auto-SCT being above the median of 3.7 months (RR 1.3, CI 95% 1.04-6.1.71, p=0.02), were associated with decreased LFS.

Outcome of patients not transplanted

Thirty-six of the 120 patients in CR after induction CT and assigned to receive SCT were not transplanted (Figure 1). Nine of them are long-term survivors, 6 of them in continuous first CR (Table 4).

Survival after diagnosis

The probabilities of overall survival and leukemia-free survival for the whole series were 37 + 4% and 38 + 4%, respectively (Figure 6). The median survival time was 17 months. Seventy-nine patients are alive and 121 have died. The probability of survival was 41 + 4% in patients ≤ 50 years old and 28 + 6% in patients >50 years old (p=0.10).

Discussion

During the last decade two important facts have emerged in AML therapy: (i) remarkably good results can be obtained in young adults with chemotherapy,[1,9,33,34] allo-SCT[9,35-40] or auto-SCT;[2,11-16,41,42] (ii) cytogenetic abnormalities at diagnosis are the strongest indicator of treatment outcome.[17-22,43] With these considerations in mind and taking into account our previous experience,[2] in 1994 we started a prospective multicenter trial for adult AML patients which included the three mentioned post-remission treatment options. We did not observe a significant improvement in CR rate by administering idarubicin instead of daunorubicin, the latter being the anthracycline used in the previous study by our group,[2] in accordance with data in recent updated reports.[6,7] However, CR was achieved more frequently after a single course of treatment in the series reported here (81% vs 63% of those achieving remission, p=0.006). Further randomized comparisons of the two mentioned anthracyclines administered at doses with best efficacy would be needed to define which is more useful in the treatment of AML.

Early relapses compromised the completion of the treatment plan in 12% of cases, this again being consistent with data from other studies.[2,11,21] The development of this complication was more likely in patients with adverse cytogenetics and/or a WBC count of >20×10^9/L at diagnosis. In these circumstances early intensified consolidation, in addition to alternative treatments such as monoclonal antibodies, would be worth investigating. Despite early relapses, it is noteworthy that 70% of patients allocated to SCT in this study received the procedure, with this proportion increasing to 78% in those ≤ 50 years old. These percentages are higher than that reported in our previous study[2] and in other similar studies.[3,12,16] The strategy of a single course of consolidation, without including high dose cytarabine, translated into low morbidity and earlier transplantation.

As observed in our previous trial, the results of auto-SCT in patients less than 50 years old were remarkably good with 60% long-term LFS and 3% TRM. These results, better than those reported in randomized studies,[3,11,15] may be due in part to the high efficacy of pre-transplant chemotherapy, which may produce *in vivo* stem cell purging thereby avoiding early regrowth of residual leukemic cells. Additionally, the use of total body irradiation might also have contributed to these good results as suggested by other authors,[11,12] although the low number of patients with adverse cytogenetics presumably facilitated the good results.

In patients older than 50 years the results of auto-SCT were poorer. When sources of progenitor cells were analyzed in this group of patients, PB grafts were associated with less TRM than were BM ones and translated into better LFS. A similar observation has been reported by the EBMT[44] and in consequence PB transplantation seems a reasonable option in this age group. Since the relapse incidence was high, allogeneic SCT using reduced intensity conditioning should be explored in this setting.[45]

Overall results with allo-SCT were better than in our previous report,[2] mainly due to decreased transplant-related mortality. T-cell depletion could have influenced this improvement, since this was the main change introduced. Despite T-cell depletion of the graft, the relapse incidence was not significantly different from that observed after unmanipulated transplants.[3,11,16]

This protocol also allowed us to evaluate the results of a non-transplant approach in patients with favorable cytogenetics. Bloomfield *et al.*[18] demonstrated the curative impact of HDAC without transplantation in this AML group. As in other studies, our results were remarkably good in patients with t(8;21), but in contrast were poor in those with inv(16). The difference in LFS between the two cytogenetic categories could be justified by a significantly higher median WBC count at diagnosis in patients with inv(16) than in those with t(8;21). Martin *et al.*[46] also reported that a high WBC count was the most significant prognostic factor indicating poor outcome in patients with inv(16). Cytogenetics, WBC count

and age were independent prognostic factors for CR achievement and also influenced early relapses and OS, the last finding being in agreement with other reports.[21,22,43] Therefore, together with cytogenetics, WBC count should be taken into account in the design of post-remission strategies for AML patients.[22]

In summary, our study shows that a strategy of single induction and consolidation, followed shortly afterwards by treatment intensification with chemotherapy or SCT, was feasible in a large number of patients. In this trial, toxicity of induction or consolidation therapy was not a major obstacle to completing the treatment plan. Early relapses were a problem in a minority of cases, being frequent in the presence of adverse cytogenetics and/or a high WBC count. These two factors were also deleterious for CR achievement and survival. HDAC seems a good strategy for patients with t(8;21) but not for those with inv(16), especially if the WBC count at diagnosis is high. As in other reports, autologous and allogeneic SCT led to similar LFS and this fact could support the strategy of avoiding the risk of TRM associated with allografting in patients with intermediate risk of relapse, directing these patients to an autologous-SCT and performing allogeneic SCT only in the case of a leukemia relapse. The source of stem cells (PB or BM) for autologous SCT appeared not to be important in AML patients up to 50 years old, whereas PB could be preferable in older patients because of the lower TRM associated with grafts of stem cells from this source. Finally, risk adapted strategies as ours seems indicated in subsequent trials. The investigation of new prognostic indicators, such as certain molecular markers and the detection of minimal residual disease may be helpful in the near future for a better stratification of the treatment based on risk factors.

SB and JS designed the study, interpreted the results and wrote the paper. JE, JB, JR, JB, JM, JB and RG recruited the patients, were the clinicians responsible for the management of the patients and acquired the data. EM, AJ and AG gave the final approval for the manuscript's submission. All the authors critically revised the manuscript

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Appendix

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