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Multicenter randomized phase II trial of idarubicin *vs* mitoxantrone, combined with VP-16 and cytarabine for induction/consolidation therapy, followed by a feasibility study of autologous peripheral blood stem cell transplantation in elderly patients with acute myeloid leukemia

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To compare the antileukemic efficacy of idarubicin and mitoxantrone in elderly patients with acute myeloid leukemia (AML) and to evaluate the feasibility of autologous transplantation using PBSC after consolidation in those with a good performance status, 160 patients (median age 69 years), with AML at diagnosis, 118 of them with *de novo* AML and 42 with AML secondary to myelodysplastic syndrome or toxic exposure (sAML), received induction treatment with idarubicin, 8 mg/m^2/day or mitoxantrone, 7 mg/m^2/day, on days 1, 3, and 5, both combined with VP-16, 100 mg/m^2/day on days 1 to 3 and cytarabine (araC), 100 mg/m^2/day, on days 1 to 7. G-CSF, 5 μg/kg/day, was administered after chemotherapy in patients aged more than 70 years. Patients in complete remission (CR) received one course of consolidation using the same schedule as for induction except the araC administration was shortened to 5 days. Some patients younger than 70 years were then scheduled for autologous stem cell harvest on days 5 to 7 of G-CSF, 5 μg/kg/day, initiated after hematopoietic recovery from consolidation. Autologous transplantation was performed following an additional chemotherapy conditioning. Ninety-five patients (59%) achieved CR, without significant difference between the idarubicin (56% CR) and mitoxantrone (63% CR) group. There was also no significant difference in CR rate between *de novo* AML (63%) and secondary AML (55%) ($P = 0.12$). Patients aged <70 years had 67% CR, while patients aged $\geqslant 70$ years had 49% ($P = 0.02$). There was no significant difference in the duration of aplasia between the two arms. Median time to neutrophil recovery was 22 days in patients who received G-CSF following induction and 27 days in patients who did not ($P = 0.006$). Severe extrahematologic toxicities of induction did not differ between the two arms and included sepsis (39%), diarrhea (13%), hyperbilirubinemia (8%), hemorrhage (6%) and vomiting (6%). Overall, 14 patients (9%), died from toxicity of induction. First consolidation was administered in 74 patients of whom seven (9%) died from toxicity. Nineteen patients have received transplantation. Median time to recovery of neutrophils $>0.5 \times 10^9$/l was 13 days and of platelets $>50 \times 10^9$/l 43 days following consolidation. There were two toxic deaths. Median disease-free survival and survival from time of achieving CR of non transplanted patients are 6 and 7 months respectively without difference between the two arms. Fourteen transplanted patients relapsed at a median of 5 months post-transplant. We conclude that this regimen is well tolerated and has a good efficacy to induce CR, without a significant difference in efficacy and toxicity between idarubicin and mitoxantrone. Intensive postinduction, including transplantation, is feasible; however, this procedure did not seem to prevent early relapse in the majority of patients. Neither the high rate of CR nor consolidation nor transplant procedure in a selected group of patients did translate into improved DFS and/or survival.

Keywords: elderly AML; treatment; triple drug induction; idarubicin *vs* mitoxantrone; PBSC transplantation

Introduction

It has been shown in a randomized comparison from the EORTC Leukemia Cooperative Group that intensive chemotherapy is beneficial to elderly patients with newly diagnosed acute myeloid leukemia (AML), leading to significantly longer survival and similar hospitalization requirements as compared to palliative treatment alone.[1] In the past, most protocols for induction were based on the combination of conventional-dose cytarabine (araC) with daunorubicin. A review of 15 studies reported between 1985 and 1992 with a total of 2255 patients older than 60 years with newly diagnosed AML revealed a median CR rate of 46% (range 28 to 58%) and toxic death rate of 30% (11 to 48%), median survival was 3 months (1.5 to 9 months) and median CR duration 10.5 months (8 to 16 months).[2] Since 1990, some randomized studies have suggested a superiority of more recent intercalating agents such as mitoxantrone[3,4] or idarubicin[5–7] to induce CR and in one study,[6] to reduce the relapse rate. The addition of VP-16 to an anthracycline-araC regimen during induction and consolidation has been shown to be beneficial for prolongation of CR.[8]

Postinduction with myeloablative cytotoxic treatment followed by bone marrow rescue has been shown to be superior to non-myeloablative chemotherapy alone for prevention of relapse in patients younger than 60 years in the large EORTC LCG-GIMEMA AML-8A trial.[9] These results were encouraging enough to try this approach in older patients. Transplant-related toxicity might be reduced by using chemotherapy-based conditioning regimens instead of total body irradiation-containing regimens.[10–12] Furthermore, the use of peripheral blood stem cells (PBSC) instead of bone marrow cells for transplantation results in a faster recovery of hematopoiesis and might decrease aplasia-related complications post-transplant.[13,14]

We report here the results of a randomized phase II trial of idarubicin and mitoxantrone in combination with araC and VP16 for induction and consolidation therapy in elderly AML, followed by a pilot feasibility study of autologous PBSC transplantation in selected patients.

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Patients and methods

Patient selection criteria

Patients aged more than 60 years, with newly diagnosed *de novo* AML or AML secondary to a preceding myelodysplastic syndrome (MDS) or to toxic exposure were eligible for this trial, provided they had a good performance status (grade 0, 1 or 2, WHO scale) and no severe organ failure.

During the first year of study, the age-limit for autologous transplantation was 70 years in selected patients. When this procedure proved to be safe and feasible, the age limit was increased to 75 years. All patients gave written informed consent before randomization for induction and consolidation.

AML was diagnosed according to FAB criteria.[15] There was no central pathology review. CR was defined by the criteria of Ellison according to the CALGB,[16] and resistant disease by the criteria of Preisler.[17] Bone marrow was assessed for response approximately 3 weeks after the end of chemotherapy, and every 3–4 months during follow-up. Relapse was defined as an increasing percentage of blasts in the bone marrow exceeding 10% or of blast cells and promyelocytes of greater than 20% in two bone marrow aspirates assessed at 2 weeks interval if in doubt. Extramedullary relapse must be confirmed by cytologic and/or histologic examinations.

All participating centers were urged to perform cytogenetics at least at diagnosis, although this was not mandatory for participation. Karyotypes were categorized according to the classification proposed at the sixth International Workshop on Chromosomes in Leukemia[18] which determined the prognosis associated with each of the specific abnormalities and complexity of karyotype in AML.[19]

Therapeutic regimen

Chemotherapy: Induction therapy included either idarubicin, 8 mg/m^2/day i.v. on days 1, 3 and 5 or, mitoxantrone, 7 mg/m^2/day i.v. on days 1, 3, and 5, according to randomization, associated with VP-16, 100 mg/m^2/day i.v. on days 1 to 3 and araC, 100 mg/m^2/day as a continuous infusion, on days 1 to 7. The dose of mitoxantrone was reduced by 1 mg as compared to the dose used in the previous EORTC AML9 study, to avoid potential toxicity induced by the addition of VP16, because a 15% death rate was observed following induction in the mitoxantrone arm of the AML9 protocol in which mitoxantrone 8 mg/m^2/day for 3 days was combined with araC but in the absence of VP16.[4] Recombinant human methionyl-G-CSF from *Escherichia coli* (filgrastim), 5 μg/kg/day i.v., was administered starting 1 day after the end of chemotherapy in all patients aged more than 70 years. Its use was also allowed in younger patients. Patients in CR after one or two courses of induction treatment received one additional course for consolidation, administered as early as possible following hematologic recovery, including the administration of G-CSF if administered during induction. In consolidation araC was restricted to 5 days. The time of neutrophil recovery corresponds to the time between start of chemotherapy (day 1) and the day PMN exceeded $>0.5 \times 10^9$/mm^3.

Stem cell transplantation: Patients treated in Lyon or Rome under the age of 70 years or, between September 1994 and July 1995, 75 years, with a performance status of 0 or 1 (WHO scale) were scheduled to undergo intensive conditioning regimen followed by autologous stem cell transplantation after one cycle of consolidation treatment. Peripheral blood stem cell (PBSC) harvest was performed by two to three aphereses beginning on day 5 of treatment with G-CSF, 5 μg/kg/day s.c., initiated within 2 weeks after hematopoietic recovery from consolidation. PBSC transplantation was first performed after conditioning with BCNU, 800 mg/m^2 i.v. on day –3.[11] Since early relapses were observed, patients thereafter were conditioned using busulfan, 4 mg/kg/day on days –6 to –3,[12] and subsequently with a more intensive regimen consisting of BCNU, 800 mg/m^2 on day –6, amsacrine, 150 mg/m^2/day, VP16, 150 mg/m^2/day, and araC, 300 mg/m^2/day, on days –4 to –2 (BAVC).[10] G-CSF, 5μg/kg/day, i.v., was administered after transplantation when neutrophil count dropped below 0.1×10^9/1 until recovery.

Supportive care: Supportive care during induction, consolidation and autologous transplantation included the use of reverse isolation or sterile room, prophylactic red blood cell and platelet transfusions, antibacterial and antifungal gastrointestinal decontamination, and the empirical use of antibiotics in case the patient became febrile.

Statistical analysis

Characteristics of patient groups were compared using Yates corrected chi square or two-tailed Fisher's exact test, when appropriate, for discrete variable and Mann–Whitney nonparametric test for continuous variables.

Complete remission rates were compared using Yate's corrected chi-square or two-tailed Fisher's exact test. 95% confidence intervals (CI) on proportions of CR patients were calculated using the exact binomial formula. Survival and DFS probabilities were calculated using the Kaplan and Meier product-limit estimate method.[20] Their 95% symmetrical CI limit was calculated according to Greenwood's method. DFS was calculated from the time of obtaining CR. Survival curves were compared using the log-rank test. For analysis of survival and DFS, patients undergoing autologous hematopoietic stem cell transplantation while in first CR were censored at the time of transplantation. Prognostic factors for CR were studied using stepwise multiple logistic regression. Prognostic factors for DFS and overall survival were studied using Cox's proportional hazard model. Statistical significance was defined as a two-tailed P value ≤ 0.05. The treatment group, and all variables that tended to be statistically (two-tailed $P < 0.1$) predictive for CR achievement, DFS or survival in the univariate analysis were proposed for entry in the mulitivariate models for prediction of the same endpoint. Quantitative variables were treated as continuous in these analyses. Goodness of fit of the models was tested using the likelihood ratio statistics. All computations were made using BMDP software (BMDP Statistical Software, Los Angeles, CA, USA).

Results

Patient characteristics

One-hundred and sixty patients entered this trial between April 1993 and February 1996. One-hundred and eighteen had *de novo* AML while 23 had AML secondary to toxic exposure and 19 resulted from transformation of a previous

Table 1 Patients characteristics at diagnosis by therapy received

Characteristics	*Patient group*	
	Idarubicin (n = 80)	*Mitoxantrone (n = 80)*
Etiology of AML		
Primary	61	57
Secondary to toxic exposure	14	9
Transformed primary MDS	5	14
Age (years)	69 (60–83)[a]	69 (60–81)
Sex (M/F)	37/43	42/38
Organomegaly[b] (y/n)	22/58	23/57
Hemoglobin (g/l)	88 (41–140)	91 (42–131)
Platelets ($\times 10^9$/l)	64 (4–994)	69 (4–1262)
WBC ($\times 10^9$/l)	5.8 (0.5–295)	6.4 (0.6–181)
Blood blasts (%)	27 (0–98)	28 (0–97)
Bone marrow blasts (%)	65 (10–99)[c]	65 (30–100)
FAB subtype		
M0	0	3
M1	18	16
M2	23	18
M3	0	0
M4	8	12
M5	18	20
M6	1	0
M7	0	0
unclassified	12	11
Cytogenetic risk group (Low/Intermediate/High)[d]	2/37/22	0/33/31
Serum LDH (μ/l; $n < 450$)	515 (139–8390)	615 (168–4326)
Use of G-CSF	43	46
Autologous transplantation	10	9

[a]Values are expressed as median (range) unless otherwise indicated.
[b]hepatomegaly, splenomegaly or extrahematologic involvement.
[c]Two cases with <30% blasts (one FAB M2, one FAB M6).
[d]Low, t(8;21), t(15;17), abn(16); high, –5/del(5), –7/del(7), +8, 11q23, t(9;22), complex abnormalitie intermediate, all others, including normal karyotypes.[18,19] None of the two low risk cytogenetic patients had at (15;17).

MDS. Twenty-three patients had AML which could not be classified according to FAB, although they met FAB criteria for AML. The patient's characteristics and treatment by randomization are listed in Table 1. There were significantly more patients with AML secondary to MDS in the mitoxantrone group, however, this was compensated by an excess of patients with AML secondary to toxic exposure in the idarubicin group. Overall, there were no differences between the two randomized groups that might have influenced the results of the analysis (*P* values, see Table 2).

Results of induction

Eighty patients were randomized to each of the two treatment groups. In approximately 76% of the idarubicin group and 80% of the mitoxantrone group chromosomal analysis was performed at diagnosis. All patients randomized were included in the analysis, although four of them (three in the idarubicin and one in the mitoxantrone group) died early, within the 7 days of induction treatment (Table 2). There was no significant difference between the idarubicin and mitoxantrone arm, with 56% (CI: 44 to 67%) and 63% (CI: 51 to 73%) of patients achieving CR, respectively. Remission was not controlled by cytogenetics. Four of five patients in whom a second course of induction was attempted attained CR in the idarubicin group, while six of 10 in the mitoxantrone group did. Conversely, the proportion of patients with resistant disease or toxic death did not differ between the two groups (Table 2). Median time to neutrophil recovery above 0.5×10^9/l and platelet recovery above 50×10^9/l following the first course of induction was 26 days (range: 10 to 46 days) and 25 days (16 to 57 days), respectively, in patients who received idarubicin, and 24 days (9 to 40 days) and 25 days (15 to 79 days), respectively, in patients treated with mitoxantrone, without significant difference between the two groups of patients. Median time to neutrophil recovery was 22 days (9 to 46 days) in patients who received G-CSF and 27 days (13 to 36 days) in those who did not ($P = 0.006$). Platelet recovery did not differ regardless of the use of G-CSF. Severe (WHO grade 3 or more) extra-hematologic toxicities of induction are reported in Table 3. They did not differ between the two arms. Most frequently severe toxicities included sepsis (observed in 39% of all patients), diarrhea (13%), hyperbilirubinemia (8%), hemorrhage (6%) and vomiting (6%). None of the cardiac toxicities observed appeared to be related to the use of idarubicin or mitoxantrone. Overall, 14 patients (9%), five of them treated with idarubicin and nine with mitoxantrone, died from toxicity of induction, mainly due to infection (Table 2).

Factors that were significantly related to failure of achieving CR in an univariate analysis (Table 4) were age ⩾70 years

Table 2 Efficacy of induction according to treatment arm

Treatment arm	*No. of patients*	*CR (%)*	*Resistant disease (%)*	*Toxic death (%)*	*Early death*[a] *(%)*
Idarubicin	80	45 (56)[b]	27 (34)	5 (6)	3 (4)
Mitoxantrone	80	50 (63)[c]	20 (25)	9 (11)	1 (1)
P		0.52	0.3	0.4	0.6
Total:	160	95 (59)	47 (39)	14 (9)	4 (3)
De novo AML	118	74 (63)			
Secondary AML	42	25 (55)			
P		0.12			

CR, complete remission.
[a]Death during 7 days of induction chemotherapy.
[b]Including four CR after two induction courses.
[c]Including six CR after two induction courses.

Table 3 Extrahematologic toxicity of first induction

Toxicity	*Number of grade ⩾3 (number of toxic deaths)*	
	Idarubicin (n = 80)	*Mitoxantrone (n = 80)*
Fever/infection	33 (4)	30 (4)
Nausea/vomiting	4	5
Diarrhea	12 (1)	9
Mucositis	3	1
Hemorrhage	5	4 (2)
Hyperbilirubinemia	7	6
Hypercreatininemia	0	1
Cardiac disorder[a]	2	3 (1)

[a]Fluid overload (four), lethal second myocardial infarction (one).

Table 4 Factors predictive for achieving CR in an univariate analysis

Factor	*No. of patients*	*CR rate (%)*	*P value*[a]
Age			
⩽70 years	91	61 (67)	0.04
>70 years	69	34 (49)	
Previous myelodysplasia			
Yes	24	9 (38)	0.02
No	136	87 (63)	
Splenomegaly			
Yes	21	8 (38)	0.05
No	139	87 (62)	
Hemoglobin level			
<80 g/l	44	29 (66)	
100 g/l	78	39 (50)	0.05
100 g/l	36	26 (72)	
Cytogenetic risk group[b]			
Low	2	2 (100)	
Intermediate	70	48 (69)	0.05
High	53	26 (49)	

[a]Yates corrected chi square or two-tailed Fischer's exact test.
[b]See legend to Table 1 for risk groups definition.

($P = 0.04$), due to a higher toxic death rate in the oldest patients (14% *vs* 4%, $P = 0.04$), preceding myelodysplasia ($P = 0.02$), initial splenomegaly ($P = 0.05$), anemia ($P = 0.05$), and the presence of cytogenetic abnormalities known to account for poor prognosis (see description of cytogenetic groups in Table 1 legend) ($P = 0.05$). Of these parameters, age ($P = 0.04$), previous myelodysplasia ($P = 0.03$), splenomegaly ($P = 0.02$) and anemia ($P = 0.03$) remained significantly predictive of poor prognosis for the achievement of CR in the multivariate analysis.

Results of post-induction

First consolidation according to the protocol was performed in 76 patients. Nineteen patients, four in the idarubicin group and 15 in the mitoxantrone group ($P = 0.04$) did not receive this consolidaton. Reasons for not undergoing consolidation did not differ according to the treatment group and included excessive toxicity of induction (11 patients), early relapse (two patients), patient refusal (two patients), loss of follow-up (one patient) and protocol violation (three patients who received lower doses of maintenance). Median time to neutrophil recovery above 0.5×10^9/l and platelet recovery above 50×10^9/l were 23 days (15 to 42 days) and 25 days (16 to 63 days), respectively, in patients who received idarubicin and 21 days (14 to 49 days) and 22 days (13 to 45 days) in those treated with mitoxantrone, without significant difference between the two groups. The most frequent extrahematologic toxicities due to consolidation were the same as for induction. Seven patients (9%), four of them treated with idarubicin and three with mitoxantrone, died from toxicity of consolidation.

Nineteen patients, representing 50% of the 38 age-eligible patients who received the first course of consolidation in the two centers performing transplants, have received autologous stem cell transplantation, one of them from bone marrow and 18 from PBSC. The median time from achieving CR to time of transplant was 3 months (2–5 months). Reasons for not undergoing transplantation included include excessive toxicity of consolidation precluding stem cell harvest for more than 3 months (five patients), early relapse, within 3 months of the end of consolidation (four patients), patient refusal (two patients), inadequate stem cell harvest (four patients) and practical reasons (four patients). Median age of transplanted patients was 69 years (range 61 to 74 years). Pretransplant conditioning used BCNU in six patients, busulfan in nine and BAVC in four. Patient were grafted with a median of 7.3 (range: 1.5 to 15) $\times 10^8$ mononuclear cells/kg containing a median of 8.3 (3.6 to 127) $\times 10^6$ $CD34^+$ cells/kg and 29.2×10^4 (5.2 to 150) CFU-GM/kg. Median duration of neutrophil recovery above 0.5×10^9/l was 13 days (9 to 21 days) and of platelet recovery above 50×10^9/l 43 days (9 to 135+ days). Severe, WHO grade 3 or more, toxicities included sepsis (eight patients), mucositis (four patients), diarrhea (two patients), vomiting, bleeding and hyperbilirubinemia (one patient each). Two patients died, one from sepsis and one from bleeding. There was no cytogenetic evaluation after successful transplantation.

At a median follow-up of 21 months, 26 patients randomized to receive idarubicin and who did not undergo autologous transplantation, relapsed after 1 to 29 months in CR while 27 patients in the mitoxantrone arm have relapsed after 0.5 to 20 months in CR.

Median DFS is 6 months in both arms with 13% (CI: 0 to 26%) and 13% (CI: 1 to 25%) of patients surviving disease-free 2 years from CR in the two groups respectively (Figure 1a). Median survival is 7 months in the two arms with 17% (CI: 7 to 27%) and 21% (CI: 11 to 31%) of patients surviving 2 years from diagnosis in the two groups respectively (Figure 1b). Four patients not undergoing transplantation are currently alive disease-free in the idarubicin arm while five are in the mitoxantrone arm. Among the 19 patients who received autologous transplantation, 14 have relapsed at a median of 5 months (range: 2 to 15 months), three are surviving disease-free (Figure 2). One of them had received conditioning with busulfan and two with BAVC. Median DFS after transplantation is 5 months and 2-year DFS is 14% (CI: 0 to 31%).

Factors predictive for short DFS in an univariate analysis were the presence of adenopathies ($P = 0.03$), cytogenetic abnormalities known to be of poor prognosis ($P = 0.003$), and hyperbilirubinemia ($P = 0.05$). High-risk cytogenetic anomalies ($P = 0.004$), hyperbilirubinemia ($P = 0.02$) and elevated serum lactic dehydrogenase (LDH) ($P = 0.01$) were predictive of short DFS in the multivariate model. Factors predictive for short survival in an univariate analysis were advanced age ($P = 0.03$), the presence of any organ involvement by the leukemia other than bone marrow and blood ($P = 0.02$), high WBC count ($P = 0.02$) and poor risk cytogenetic abnormalities ($P = 0.02$). Advanced age ($P = 0.02$), high WBC count ($P = 0.03$) and poor risk cytogenetic abnormalities were predictive of short survival in the multivariate analysis. Univariate and multivariate analyses were performed only for relapse, not for toxic deaths. This statistical analysis concerns, therefore not all, but 72 patients.

Discussion

Our study shows the feasibility and efficacy of a chemotherapy regimen using adapted doses of new intercalating agents such as idarubicin and mitoxantrone in association with VP-16 and araC to induce CR in elderly patients with newly diagnosed AML, without differences in efficacy or toxicity between idarubicin and mitoxantrone. However, numbers are too small and the follow-up too short to be able to

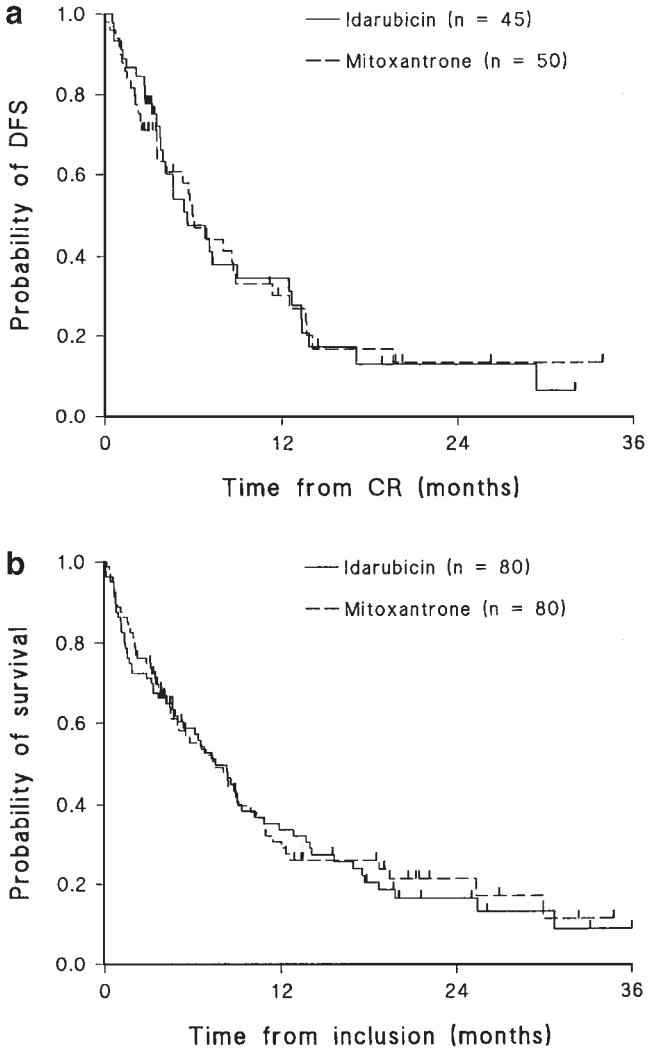

Figure 1 Disease-free survival (a) and survival (b) according to randomization arm.

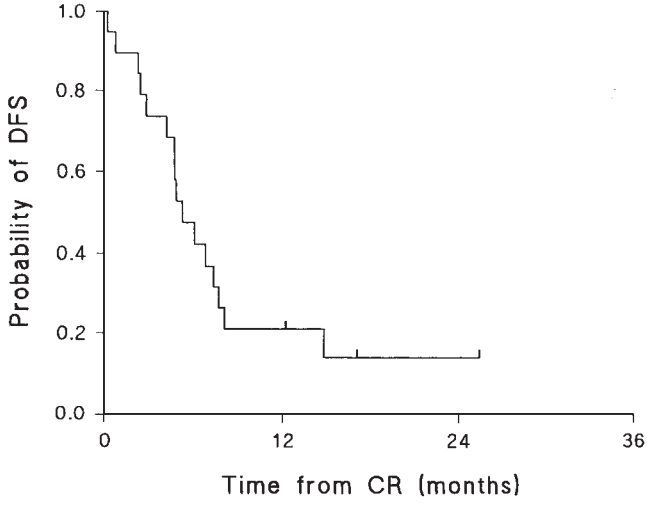

Figure 2 Disease-free survival after transplantation of the 19 patients who underwent autologous transplantation.

detect a clinically meaningful difference. Still this is the first study reported (except for abstracts) of a direct comparison between these two anthracyclines. The 59% CR rate achieved in our 160 patients with a median age of 69 years with *de novo* or secondary AML compares favorably to that reported in studies recently published in unselected elderly AML patients, which ranges from 42% to 55%.[4,21–25] The previous EORTC AML9 and AML 11 studies, which targeted the same patient population using mitoxantrone or daunorubicin in combination with standard-dose araC for induction and consolidation therapy had an overall CR rate of 42% and 55% respectively.[16,22] Although the overall survival in the present study is not better, CR rate in our *de novo* AML patients was 63%.

The encouraging CR rate observed in our trial might be due to the use of recent intercalating agents since idarubicin as well as mitoxantrone have been shown to induce CR more often than daunorubicin in patients with AML.[3–7] A recent study comparing idarubicin and daunorubicin in patients with *de novo* AML older than 55 years showed no difference between the two drugs, although there were less resistant patients in the idarubicin arm.[26] The contribution of VP16 in achieving CR is also possible. However, two large randomized studies have shown no increase in CR rate when VP16 was used,[8,27] and the Australian study clearly showed that VP16 was poorly tolerated in the elderly. Therefore, the doses of either idarubicin or mitoxantrone were attenuated in our study. Another reason for the improved CR rate in our study might be the low treatment-related death rate. The death rate during aplasia in our 160 patients during induction was 9% while in previous trials it ranged from 15 to 29% in patients treated with idarubicin combined with araC[6,7,26,28] and from 14% to 15% in patients who received mitoxantrone combined with araC.[3,4] Except for the EORTC AML 9 study,[4] all these trials used significantly higher doses of mitoxantrone or idarubicin than our trial. Taken together, these results could indicate that the addition of VP16 to an intercalating agent plus araC, allows the dose of intercalating agent to be diminished and reduces the overall toxicity of this regimen without impairing the antileukemic efficacy of induction.

Despite a good tolerance of our regimen and the use of G-CSF in all patients aged ⩾70 years, the toxic death rate was higher in this patient group. The use of G-CSF during chemotherapy-induced aplasia in AML led to a more rapid neutrophil recovery (for review see Ref. 29). Also, it has been shown to increase CR rate in two recent trials in elderly AML. However, in both trials, this effect appeared related to a decrease of resistant cases rather than of toxic death and did not result in longer DFS or survival in G-CSF-treated patients.[30,31]

Consolidation chemotherapy using reduced dosages of araC could be administered to most patients in CR. However, seven toxic deaths were observed. DFS remained short despite the use of VP16. The addition of VP16 had been decided because it had been shown to increase DFS in a randomized AML trial.[8] In that study, the effect of VP16 was explained by a reduction of relapse rate in patients younger than 55 years, while the relapses in older patients remained unaffected.

Intensive chemotherapy conditioning followed by autologous stem cell rescue could be administered safely to 50% of patients having undergone the first consolidation and being eligible according to their age. The use of autologous stem cell transplantation is generally restricted to younger patients. The extension of this procedure to older age groups might be possible using less intensive conditioning regimens.[11,12] Conditioning in 15 of our autografted patients used BCNU or bus-

ulfan alone. They had been previously used as single-agent conditioning prior to autologous transplantation in glioma patients[11] and in chronic myelocytic leukemia,[12] respectively. Due to frequent relapses following the autograft when these conditionings were used in our AML patients, we switched to BAVC, a multidrug schedule which has been already used in younger AML patients, showing results similar to those achieved with more toxic regimen.[10] Nevertheless, early relapses post-graft still occurred, although we have not autografted a sufficient number of patients after BAVC conditioning to precisely assess the relapse rate.

It is a general finding that increasing the intensity of induction and postinduction in elderly AML patients does not result in prolongation of CR duration as it has been observed in younger patients.[6,32,33,34] In part, this is due to increased toxicity in elderly patients. However, it might also be due to the high frequency of poor prognostic cytogenetic defects in elderly AML, since intensification of therapy including autologous or allogeneic transplantation in young patients, is much less effective in preventing relapse in poor prognostic cytogenetic subgroups.[35,36]

In summary, our data are encouraging. However, we realize their limitations because they are obtained from small subgroups of patients, and they may not hold out with longer follow-up. However, they clearly show the feasibility that selected patients in an elderly population can tolerate more aggressive chemotherapy for treating AML.

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