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ORIGINAL ARTICLE

Consequent and intensified relapse therapy improved survival in pediatric AML: results of relapse treatment in 379 patients of three consecutive AML-BFM trials

A Sander[1], M Zimmermann[1], M Dworzak[2], G Fleischhack[3], C von Neuhoff[1], D Reinhardt[1], GJL Kaspers[4] and U Creutzig[5]

[1]Department of Pediatric Hematology/Oncology, Medical School Hannover, Hannover, Germany; [2]Children's Cancer Research Institute and St Anna Children's Hospital, Vienna, Austria; [3]Department of Pediatric Hematology/Oncology/, Children's Hospital Medical Center, University of Bonn, Germany; [4]Department of Pediatric Hematology/Oncology, VU Medical Center, Amsterdam, The Netherlands and [5]Department Hematology/Oncology, University of Muenster, Muenster, Germany

Relapse remains the major cause of treatment failure in pediatric acute myeloid leukemia (AML). We analyzed the clinical characteristics, treatment response to relapse treatment and overall survival (OS) of 379 children with AML relapse treated according to three consecutive frontline protocols of the AML-Berlin/Frankfurt/Muenster study group (AML-BFM-87/-93/-98). Of 313 treated patients with data on remission status, 198 children (63%) achieved a second complete remission (CR2). There were no significant differences in remission rates and OS for the intensive reinduction treatment schedules used. The 5-year OS rate was 23% for the total group and 29% for patients treated with curative intent. OS rates increased with study periods from 18 to 34% ($P_{log\ rank} = 0.012$), whereas the proportion of patients receiving only palliative treatment decreased from 23 to 11% ($P_{CMH} = 0.005$). Late relapse, no allogeneic stem cell transplantation (SCT) in CR1, age <10 years and favorable cytogenetics were independent favorable prognostic factors for survival. Achievement of CR2 was the most important prognostic factor (OS 44 vs 3%; $P_{log\ rank} < 0.0001$). Overall, one-third of children with relapsed AML can be cured today. SCT in CR2 is recommended for most patients, although its impact on CR2 is discussed.
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Keywords: pediatric acute myeloid leukemia (AML); relapse; chemotherapy; stem cell transplantation; prognostic factor

Introduction

Long-term survival rates in pediatric acute myeloid leukemia (AML) have been markedly improved by intensification of first-line treatment and better supportive care with overall survival (OS) rates increasing from 40 to 60% during the past two decades.[1,2] However, relapse remains a major obstacle for improving prognosis further. Survival after recurrence was poor so far, ranging from 21 to 33%.[3–6] The duration of first complete remission (CR1) has been reported to be the major prognostic factor in relapse with a 5-year survival of only 10% in early relapse defined as relapse occurring within 12 months after diagnosis.[5] French–American–British (FAB) subtypes as well as cytogenetics and intensity of first-line treatment including allogeneic stem cell transplantation (allo-SCT) are well recognized as additional prognostic factors in the relapse setting.[4,7,8] Allo-SCT in CR2 has been associated with a 5-year OS rate of 62% in recent studies.[9]

Correspondence: Dr A Sander, Department of Pediatric Hematology and Oncology, Medical School Hannover, Carl-Neuberg Str. 1, D-30625 Hannover, Germany.
E-mail: sander.annette@mh-hannover.de
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From 1987 to 2003, a total of 1251 patients with *de novo* AML were registered in three consecutive protocols of the AML-Berlin/Frankfurt/Muenster study group (AML-BFM-87, AML-BFM-93, AML-BFM-98), of whom 379 patients relapsed between 1987 and 2007. In this study, we analyze the outcome after relapse in this cohort on the basis of the intensity of first-line treatment, including allo-SCT or autologous SCT (auto-SCT), duration of first remission, modalities of relapse treatment and achievement of a second complete remission (CR2).

Patients and methods

Patients

Of a total of 1251 pediatric patients with *de novo* AML aged ⩽18 years registered in AML-BFM-87, AML-BFM-93 and AML-BFM-98, 379 children relapsed until October 2007. Two additional relapsed patients were registered during this period, but excluded from analysis as one of them presented with an immunophenotype of AML including coexpression of lymphatic antigens (such as CD19 and TdT) at initial diagnosis and also presented with common acute lymphoblastic leukemia at relapse, whereas the other patient developed secondary acute lymphoblastic leukemia after AML.

First-line treatment

The intensity of first-line treatment was increased from AML-BFM-87[10] to AML-BFM-93/-98 (see Figure 1).[11–13] Allo-SCT from a matched sibling donor was recommended for high-risk patients in CR1 only.

Relapse treatment

Relapse treatment was heterogeneous until 1997. The first AML-BFM relapse protocol started in 1991 (AML-BFM-REZ-91) and consisted of two reinduction cycles containing mitoxantrone and etoposide, followed by allo- or auto-SCT. The subsequent protocol, AML-BFM-REZ-93, included high-dose cytarabine and mitoxantrone (HAM) for second induction, followed by auto-SCT and 12 months of maintenance therapy. Both trials were multicenter trials; however, patient recruitment was low because numerous patients received elements from upfront treatment protocols, alternative regimens, palliative or no treatment. From 1997 to September 2001, treatment according to the AML-BFM-REZ-97 protocol was recommended comprising a double induction regimen with intermediate-dose cytarabine and liposomal daunorubicin, followed by a 6-week consolidation with thioguanine, low-dose cytarabine and allo- or auto-SCT.[14] Alternatively or after nonresponse (NR) to this regimen,

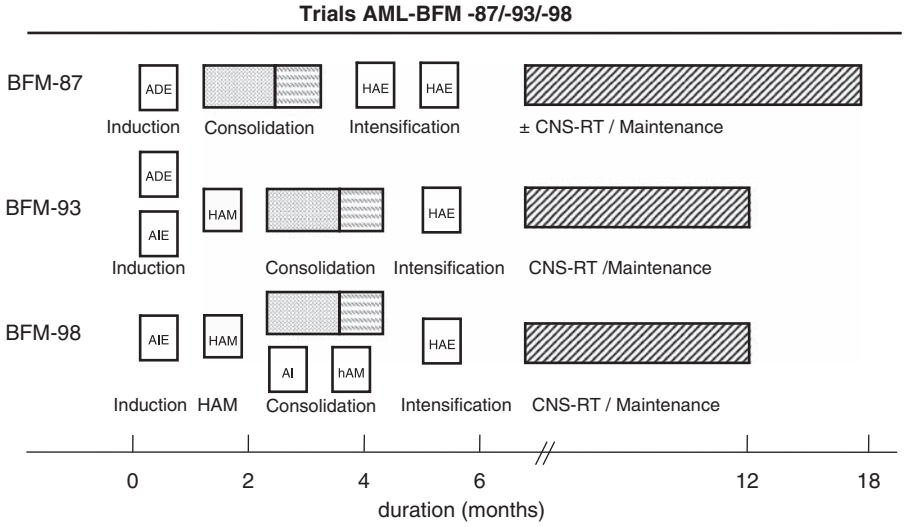

Figure 1 Protocol flow chart of first-line treatment. BFM: Berlin Frankfurt Münster; ADE: cytarabine, doxorubicin, etoposid; AIE: cytarabine, idarubicin, etoposid; HAM: high-dose cytarabine, mitoxantrone; AI: cytarabine, idarubicin; hAMi: intermediate-dose cytarabine, mitoxantrone; HAE: high-dose cytarabine, etoposid; CNS: central nervous system; RT: radiation therapy.

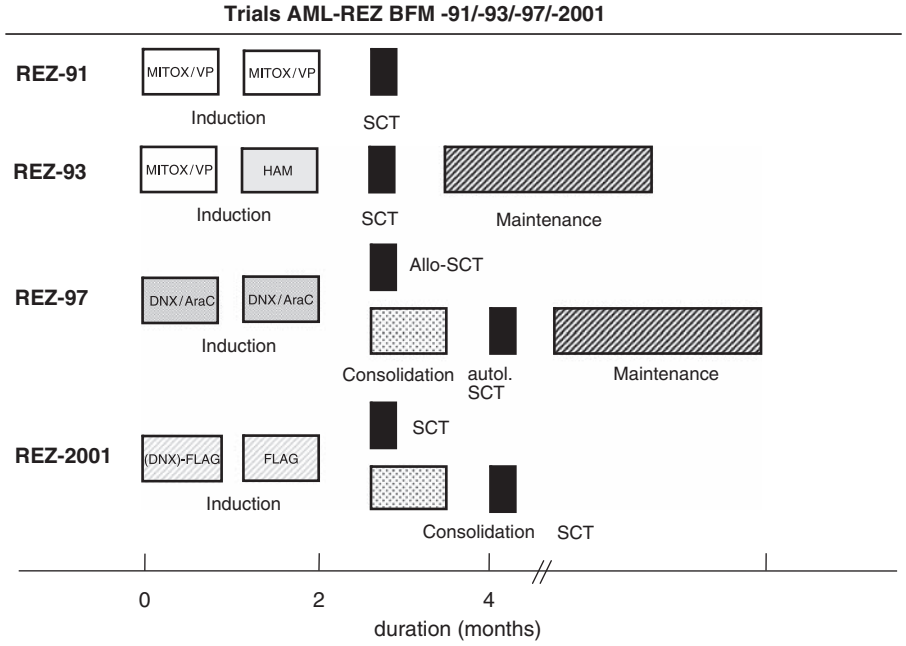

Figure 2 Protocol flow chart of trials AML-BFM-REZ-91, AML-BFM-REZ-93, AML-BFM-REZ-97 and Relapsed AML 2001/01. BFM: Berlin Frankfurt Münster; CNS: central nervous system; RT: radiation therapy; HAM: high-dose cytarabine, mitoxantrone; SCT: stem cell transplantation; MITOX: mitoxantrone; VP: VP16; HAM: high-dose cytarabine, mitoxantrone; DNX: liposomal daunorubicine; FLAG: fludarabine, cytarabine, G-CSF.

IDA-FLAG (idarubicin, fludarabine, cytarabine, granulocyte-colony-stimulating factor) and FLAG were administered according to a phase II study protocol.[15] In the recently closed, international protocol, Relapsed AML 2001/01, the impact of liposomal daunorubicin in combination with FLAG on remission rates and long-term cardiotoxicity was evaluated (protocol flow charts see Figure 2, for details see Supplementary Table S1). Treatments classified as 'other' were heterogeneous approaches and included allo-SCT without previous reinduction in 6 patients, 6-week consolidation as initial therapy in 4 patients, elements from acute lymphoblastic leukemia protocols in 2 patients, intrathecal triple chemotherapy in 5 patients and intrathecal combined with central nervous system irradiation in 3 patients. Two patients with relapsed acute promyelocytic leukemia received arsenic trioxide.

Definitions

Relapse. Morphologically, $\geqslant$5% of leukemic cells in the bone marrow (BM) and central nervous system relapse $\geqslant$5 leukemic cells per µl in the cerebrospinal fluid.

Remission. $<$5% blasts on morphological examination of a nonhypoplastic BM and recovery of granulopoiesis and

megakaryopoiesis with an absolute neutrophil count >1000 per μl and platelet count >50 000 per μl in the peripheral blood, without any signs of leukemia elsewhere.

NR after relapse treatment. Persistence of ⩾20% of leukemic blasts in the BM after two cycles of chemotherapy.

Partial response. Blast count >5% and ⩽20% in the BM or BM hypoplasia without recovery of the peripheral neutrophil (absolute neutrophil count >1000 per μl) and platelet count (>50 000 per μl without transfusion).

Early death. Death within 42 days from diagnosis.

Statistics

OS was calculated from the date of diagnosis of relapse to death of any cause or last follow-up. The Kaplan–Meier method[16] was used to estimate survival rates with comparisons based on the two-sided log-rank test. Estimates of survival are given as probability of 5-year survival (pOS) ± standard error (s.e.). Cox proportional hazards model was used for multivariate analyses of survival, and logistic regression was used for the analysis of prognostic factors for CR after relapse. Stepwise variable selection was performed to select variables included in the models. For variable selection, the variable entry and removal significance levels were 0.10. Differences in the distribution of individual parameters among patient subsets were analyzed using the χ^2 test or Cochran–Mantel–Haenszel (CMH) test for categorized variables and the Mann–Whitney *U*-test for continuous variables. All *P*-values are two sided and were considered significant when <0.05. Statistical analyses were conducted using the SAS program (SAS-PC, Version 9.1, SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The cumulative incidence of relapses in the AML-BFM studies was 30% and not significantly different between the three studies (31 vs 28 vs 31%). Patient characteristics (such as age, sex, FAB type, cytogenetics and risk-group classification) during first-line treatment were equally distributed over the three study populations and are shown in Table 1. In 193 out of 379 patients (51%), relapse occurred early within 1 year from initial diagnosis, whereas 186 patients (49%) developed late relapses. Median time to relapse was 11.7 months. Relapses occurred mainly in the BM (92%), combined or isolated in the central nervous system (15%) and other extramedullary sites (6%). Overall, 27% of all patients with relapse had been stratified to the standard-risk and 73% to the high-risk group at initial treatment according to morphology and early treatment response at day 15.[17] Most of the relapsed patients were treated with chemotherapy only in CR1 ($n=336$, 88%), 43 patients (11%) were transplanted in CR1 ($n=36$, (9%) with allo-SCT; $n=7$, (2%) patients with auto-SCT).

Treatment results

In all, 304 of a total of 379 patients with relapse (80%) received intensive chemotherapy consisting of either elements from upfront protocols or specific relapse protocols, 21 (5%) received other treatments and 52 (14%) were offered no or palliative

Table 1 Characteristics and outcome of 379 patients with AML relapse

	N	%	5-y OS (%)	P-*value*
Total group	379	100	23	
Initial protocol				
AML-BFM-87	97	26.5	18	
AML-BFM-93	133	35.1	23	0.065
AML-BFM-98	149	39.3	31	
Age (years)				
<10	205	54.1	26	
⩾10	174	45.9	22	0.89
Median age	9.2			
Gender				
Male	226	59.6	24	
Female	153	40.4	25	0.92
FAB type				
M0	17	4.5	6	
M1	49	12.9	24	
M2	86	22.7	23	
M3	9	2.4	44	0.0034
M4	69	18.2	35	
M5	109	28.8	26	
M6	13	3.4	23	
M7	27	7.1	4	
Relapse site				
isolated BM	301	79.4	25	
BM+CNS	37	9.8	17	0.076
CNS	20	5.3	40	
Extramedullary	21	5.5	13	
Cytogenetics				
t(8;21)	21	7.6[a]	33	
t(15;17)	6	2.1[a]	33	
inv(16)	15	5.4[a]	47	
11q23	61	22.2[a]	24	0.071
Complex[b]	6	2.1[a]	33	
Normal	58	21.1[a]	31	
Other	108	39.3[a]	23	
No data	104	27.	17	
Risk group stratification				
SR	99[c]	26.1	36	
HR	280[c]	73.9	21	0.0004
Time to relapse from diagnosis (years)				
<1	193	51	13	
⩾1	186	49	37	<0.0001
Consolidation in CR1				
Chemotherapy	336	88.6	26	
SCT				
Auto-SCT	7	1.8	0	
Allo-SCT	36	9.5	13	0.0012
Achievement of CR2				
CR2	198	63.2	44	
No CR2	115[d]	36.7	3	<0.0001
Consolidation in CR2				
Chemotherapy	45	11.9	35	
SCT (auto- and allo-SCT)	153	40.4	46	0.11

Abbreviations: allo-SCT, allogeneic stem cell transplantation; AML-BFM, AML-Berlin/Frankfurt/Muenster; auto-SCT, autologous stem cell transplantation; BM, bone marrow; CNS, central nervous system; CR1, first complete remission; CR2, second complete remission; FAB, French–American–British; HR, high risk; OS, overall survival; SR, standard risk.
[a]Percentage related to $n=275$ patients with data on cytogenetics.
[b]Defined as three cytogenetic alterations of which at least one structural alteration or >3 numeric alterations.
[c]Defined as favorable FAB type and BM blast count <5% on day 15, patients of study AML-BFM-87 were stratified retrospectively.
[d]$n=51$ patients with no or palliative treatment are excluded.

Table 2 Response to relapse therapy

Therapy	n = *379*	*No response data (%)*	*ED (%)*	*NR (%)*	*PR (%)*	*CR (%)*	*Five-year-OS (%)*
None	37	0	6	94	0	0	0
Palliative	15	0	7	86	7	0	0
Reinduction (elements from upfront protocols)	83	5	2	36	13	43	20
AML-BFM-REZ-91	14	7	7	14	14	57	29
AML-BFM-REZ-93	37	5	0	35	3	57	27
AML-BFM-REZ-97	63	6	0	35	0	59	23
FLAG, IDA-FLAG, DNX-FLAG[a]	107	0	1	19	2	78	40
Other (Consolidation, ALL, Triple IT, Arsenic)	21	4	4	32	4	55	29
No data on regimen	2	100	0	0	0	0	0

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin Frankfurt Münster; CR, complete remission; DNX, liposomal daunorubicine; ED, early death; FLAG, fludarabine, cytarabine, granulocyte-colony-stimulating factor; Ida, idarubicin; IT, intrathecal; NR, nonresponse; OS, overall survival; PR, partial response; REZ, relapse.
[a]Including 71 patients of the International Relapsed AML2001/01 trial.

treatment. In two patients, no data on relapse treatment were available.

Overall, the CR2 rate was 54% for the total group (198 out of 365 patients with data on remission status) and 63% for 313 patients with data on remission status treated with curative treatment intent. There were no significant differences in remission rates and OS for the intensive reinduction treatment schedules used (Table 2). Nevertheless, there was a trend toward improved CR2 rates among the consecutive studies with 78% of patients achieving CR2 with the most recent FLAG-based regimen. Remission rates after relapse increased also within the first-line study periods (AML-BFM-87: 49%, AML-BFM-93: 63%, AML-BFM-98: 72%, $P_{CMH} = 0.001$; patients with no or palliative treatment were excluded). Simultaneously, the number of patients with no or only palliative treatment decreased from study period AML-BFM-87 (23%) to studies AML-BFM-93/-98 (11%), $P_{CMH} = 0.005$.

The rate of early deaths was low (2%), whereas treatment-related death occurred in 14% of the patients ($n = 47$). Treatment-related death was similar in early and late relapses (13 vs 15%, respectively, P_{Gray} 0.71) whereas NR and second relapse were more frequent in patients with early relapse (72 vs 44%, respectively, $P_{Gray} < 0{,}01$).

The 5-year OS rate for the total group was $23 \pm 3\%$ and $29 \pm 3\%$ for patients treated with curative intent. Despite a constant relapse rate after first-line treatment, OS after relapse increased over time within the first-line study periods from $18 \pm 4\%$ (AML-BFM-87) to $21 \pm 4\%$ (AML-BFM-93) and to $31 \pm 4\%$ (AML-BFM-98), $P_{\log\ rank} = 0.012$ (total group; Figure 3). This was also seen when patients with no or only palliative treatment were excluded from analysis (OS (AML-BFM-87) $23 \pm 5\%$; (AML-BFM-93) $26 \pm 4\%$ and (AML-BFM-98) $34 \pm 4\%$).

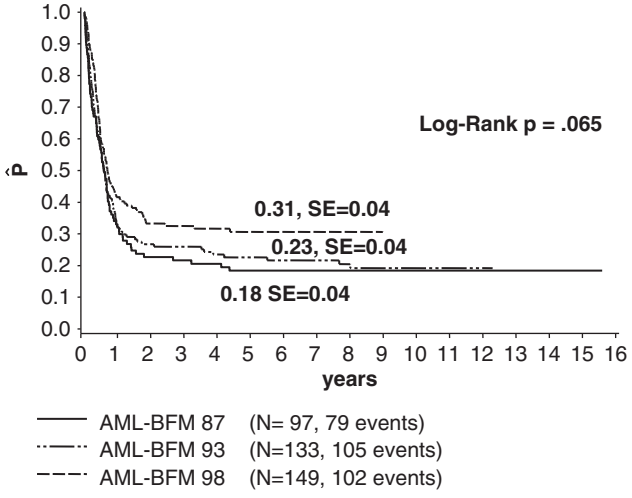

Figure 3 Probability of survival in 379 patients with AML relapse according to initial therapy trials AML-BFM-87, AML-BFM-93 and AML-BFM-98.

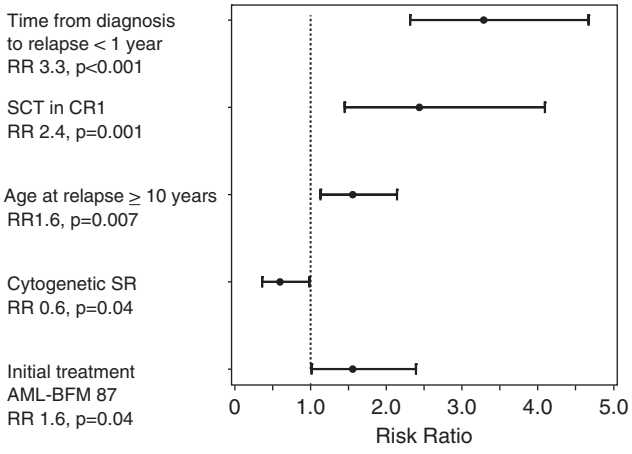

Figure 4 Probability of survival in 379 patients with AML relapse according to initial therapy trials AML-BFM-87, AML-BFM-93 and AML-BFM-98.

Prognostic factors

In multivariate Cox regression analysis including age at relapse, gender, time to relapse, FAB-type (M1, M2, M5, M7), cytogenetic risk group at diagnosis, risk stratification for and study period of first-line treatment, only time to relapse (>1 year), age <10 years at relapse, favorable cytogenetics and no SCT in CR1 were independent favorable prognostic factors regarding achievement of a second CR (logistic regression) and survival (Cox regression) (Figure 4). For patients who had achieved CR2, only time to relapse remained a significant risk factor. Patients with a short duration of first remission (<1 year from diagnosis) had a significant worse outcome than did those with CR1 duration of ⩾1 years (5-year OS $13 \pm 2\%$ vs $36 \pm 4\%$, $P_{\log\ rank} < 0.0001$).

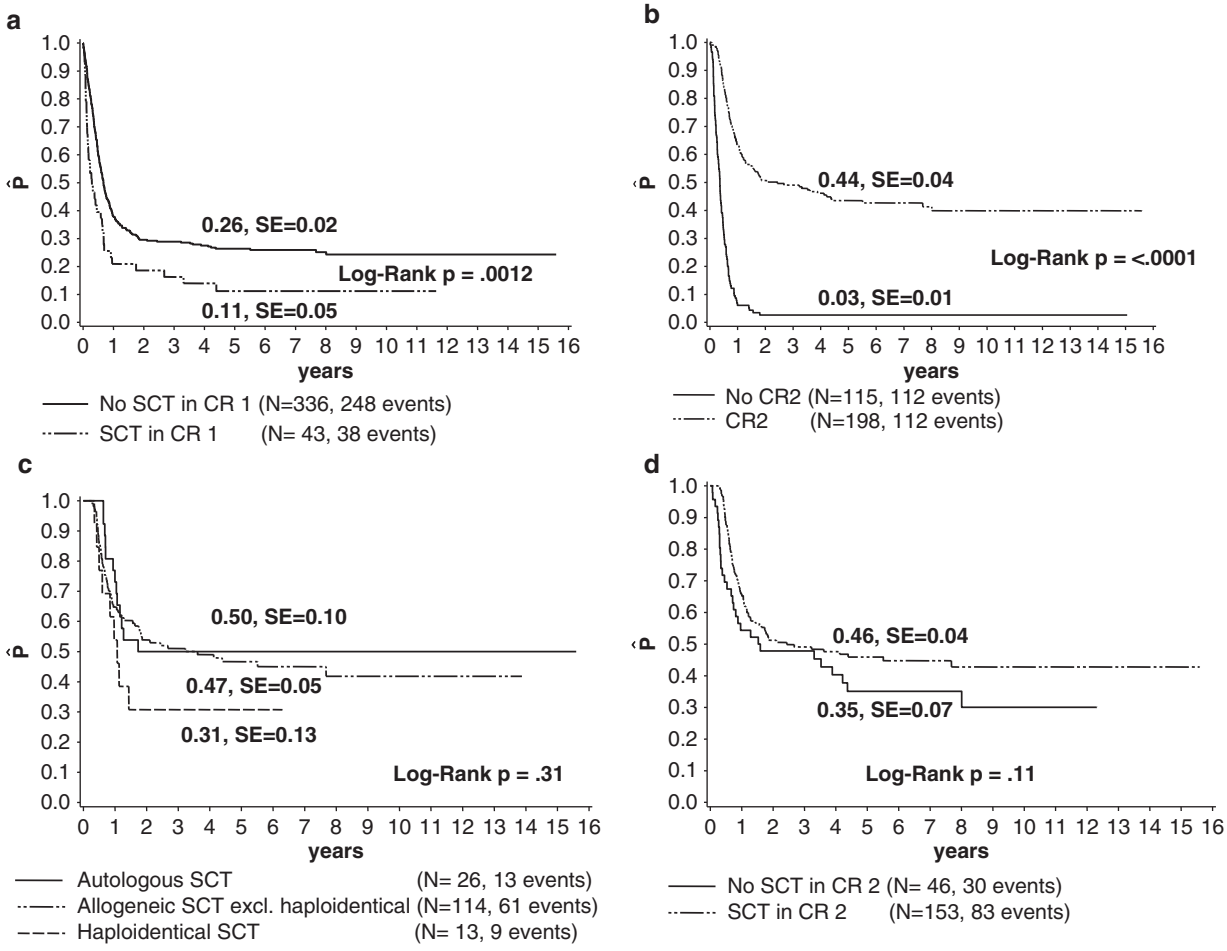

Figure 5 (**a**) Probability of survival according to postremission therapy in CR1. (**b**) Probability of survival according to remission status after relapse. (**c**) Probability of survival according to transplant type in CR2. (**d**) Probability of survival according to postremission therapy in CR2. SCT: stem cell transplantation; CR1: first complete remission; CR2: second complete remission.

Remission rates were significantly lower in patients who underwent SCT in CR1 ($n=43$) than in those who received chemotherapy alone ($n=322$) (34 vs 57%, $P_{chi^2} = 0.005$). This finding was even more obvious in patients with late relapse (41 vs 72%, $P_{chi^2} = 0.003$), but not significant in those with early relapse (26 vs 43%, $P_{chi^2} = 0.164$). However, 14 of 43 (32%) early relapsed patients with SCT in CR1 received only palliative or no relapse treatment. Accordingly, the 5-year OS rate after relapse was significantly lower in patients who received SCT in CR1 when compared with those who were treated with chemotherapy alone ($11 \pm 5\%$ vs $26 \pm 2\%$, $P_{log\ rank} = 0.0012$) (Figure 5a). Overall, achievement of CR2 was the most relevant predictor of survival (5-year OS: $44 \pm 4\%$ in CR2 patients vs $3 \pm 1\%$ in NR) (Figure 5b).

SCT after relapse

In total, 153 of 198 (77%) patients in CR2 received SCT (127 allogeneic, including 13 haploidentical and 26 autologous). There were no differences in the proportion of patients who received SCT in CR2 within the different study periods (AML-BFM-87: 81% vs AML-BFM-93: 69% vs AML-BFM-98: 81%, $P_{CMH} = 0.59$). However, the percentage of allo-SCT from related, and in particular from unrelated, donors compared with auto-SCT increased (allo-SCT in CR2: AML-BFM-87: 15% vs AML-BFM-98: 51%). Median time to transplant was 105 days. OS was comparable among the different SCT types (allogeneic $47 \pm 5\%$ vs haploidentical $31 \pm 13\%$ vs autologous $50 \pm 10\%$ $P_{log\ rank} = 0.31$) (Figure 5c), with a higher 5-year OS rate after SCT in patients with late relapses (allogeneic including haploidentical $51 \pm 6\%$ vs autologous $58 \pm 11\%$ $P_{log\ rank} = 0.54$) than in those with early relapse (allogeneic including haploidentical $33 \pm 7\%$ vs autologous $29 \pm 17\%$; $P_{log\ rank} = 0.85$). The distribution of auto- and allo-SCT in early and late relapses was comparable: auto-SCT, 27% in early and 73% in late relapses, allo-SCT, 35 and 65%, respectively, $P_{chi^2} = 0.2$. Haploidentical SCT was performed in 13 patients in CR2 and in 5 patients with blast persistence. In all, 4 of the 13 patients in CR2 and none of the patients who did not attain CR2 survived. Overall, 14 of 43 patients (32%) who had been transplanted in CR1 received a second SCT. Out of 12 patients with late relapse in this group, 3 survived.

Comparison of postremission therapies in CR2 showed no significant difference in survival between patients who underwent SCT (including auto-SCT) and those who were treated with chemotherapy only (Figure 5d). The corresponding 5-year OS rates were $46 \pm 4\%$ after SCT vs $35 \pm 7\%$ without SCT ($P_{log\ rank} = 0.11$).

Discussion

To our knowledge, the cohort of 379 patients with relapsed AML presented in this study is the largest group of patients with relapse of pediatric AML that has been reported to date.

Five-year OS rates after first AML relapse have increased from 18 to 31% during the past two decades, most certainly because of uniform curative treatment concepts according to AML-BFM relapse protocols, including increased intensity of reinduction therapy, and because of improved supportive care regimens. Comparable observations have been reported by other groups: A 3-year OS rate of 24% after relapse was reported for treated and untreated pediatric patients from the MRC (Medical Research Council) AML10 trial.[6] The 5-year OS was 34% in 146 patients from the NOPHO (Nordic Society for Pediatric Hematology and Oncology) studies[9] and 33% in 106 patients treated within the French LAME (Leucémie Aiguë Myéloblastique Enfant) 89/91 protocol.[3] Data from the St Jude institutional trials showed a 5-year OS of 23% in 160 relapse patients.[4]

Within the AML-BFM study periods (Figure 1), CR and survival rates after first relapse improved despite the intensification of first-line induction therapy. This improvement could not be related to the type or the intensity of relapse chemotherapy, which might result from the heterogeneity of relapse treatment and the low numbers of patients treated according to the different regimens. However, response rates increased with consistent and intensified reinduction courses, reaching 78% with the current standard regimens with FLAG and anthracyclins. The trend toward increased efforts for cure and improved treatment over time is also reflected by the fact that patients from the AML-BFM-87 trial showed the worst outcome after relapse and by the decreasing number of patients who were offered no or only palliative treatment in our studies.

The main prognostic factors for survival after relapse in our studies were duration of first remission and response to relapse treatment, which has been reported previously by our study group[5] and others.[3,4,9]

Our data regarding age, FAB type and cytogenetics as prognostic factors after relapse are in line with others. Webb *et al*.[18] analyzed the effect of age and clinical features on survival in childhood AML and did not find any relationship between age and CR rates, but a significant adverse effect of increasing age, adverse cytogenetic and FAB type other than M5 on the risk of relapse. FAB M5 correlated with a high risk of relapse in the study reported by Rubnitz *et al*.[4] A favorable outcome in patients with t(15;17), inv(16) and t(8;21) was reported by Grimwade *et al*.[7]

Intensification of first-line postremission therapy with allo-SCT led to lower remission and survival rates after relapse when compared with the results after chemotherapy alone and revealed to be an independent negative prognostic factor for survival after relapse in the multivariate analysis. This has also been reported by the St Jude group[4] and the NOPHO group (5-year OS $18 \pm 9\%$ for patients with relapse after SCT in CR1).[9]

Patients who achieved CR2 had similar survival rates after different modalities of postremission therapy, including chemotherapy alone (Figures 5c and d). Comparable survival rates after chemotherapy alone have also been reported by Goemans *et al*.[19] for 10 of 41 relapsed Dutch pediatric AML patients. However, the interpretation of these results is limited because of small patient numbers. Patients assigned to a consolidation with chemotherapy only in CR2 of the cohort presented in this study often suffered late or isolated relapses. Hence, there seems to be a selection bias when comparing them with the SCT group. Reports on allo-SCT in CR2 in children from other groups showed 5-year survival rates from 49% up to 62%, depending on transplant type and donor.[9,20,21]

In the era of graft engineering and improved methods of immunosuppression, most groups have abandoned auto-SCT. Our retrospective analysis included data of 26 patients who underwent auto-SCT in CR2, mostly from former East-German centers that had favored this approach. Results show comparable OS rates with auto- and allo-SCT (including haploidentical SCT) especially for late relapses (OS 58 vs 51%, $P = 0.022$). Considering the small number of patients in the autologous group, implications of these results are limited but may indicate that auto-SCT can be an alternative to haploidentical SCT in late AML relapse, if a matched donor is not available. Results of auto-SCT have also been reported by Godder *et al*.[22] who found a 3-year OS of 60% in patients with late relapses, whereas OS was only 23% in patients with early relapses. Although the value of allo- or auto-SCT compared with chemotherapy only in postremission in CR2 has not been proven by randomized trials, SCT is still recommended for most patients as it provides an additional, more intensive treatment option, when compared with conventional chemotherapy.

Survival after SCT in CR1 and relapse is poor. Treatment options for these patients have been reviewed by Shaw and Russell.[23] They concluded that the main strategies aim at achieving CR by disease-directed therapy and at exploiting the graft-versus-leukemia-effect by immunomodulatory interventions, such as donor lymphocyte infusion (DLI). However, these conclusions were based on small patient numbers in various studies or on retrospective data analyses from registries. Again, time to relapse and achievement of remission were confirmed to be important prognostic factors in this setting.[24–26] Second SCT should be considered especially for patients with late relapses who achieved CR2.[27]

Patients who did not achieve CR2 had a very poor outcome. Even after early allo-SCT, the 5-year survival rate was only 3%. This observation indicates that specific and highly sensitive methods are required to predict NR as early as possible and new therapeutic strategies including new drugs and new methods of SCT are required for these patients.

Conclusions

Survival after relapse has clearly improved over the past two decades with the availability of standardized relapse treatment protocols and improved supportive care. Achievement of a CR2 remains the most important prognostic factor after AML relapse. Once CR2 is achieved, SCT is recommended for most patients. Additional biological and/or clinical markers promoting risk-group identification and risk-adapted stratification of relapse therapy are required. Patients who do not respond to relapse treatment have a very poor outcome. The development of more sensitive methods to identify potential NR and new therapeutic options are urgently warranted for these patients.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Leukemia website (http://www.nature.com/leu)