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Outcome for children with relapsed acute myeloid leukemia in the Netherlands following initial treatment between 1980 and 1998: survival after chemotherapy only?

We report the outcome of Dutch pediatric relapsed AML patients and focus on patients treated with chemotherapy alone. Median time from first complete remission to relapse was nine months. Second complete remission (CR2) was achieved in 63%. Overall, only 16% of patients were survivors. When only patients who achieved CR2 were analyzed, 50% of the patients treated with allogeneic stem cell transplantation and 24% of the patients treated with chemotherapy alone, were long-term survivors.

The prognosis of children with acute myeloid leukemia (AML) has improved markedly over the last decades with 5-year overall survival rates (5-year pOS) in the most recent treatment protocols as high as 50-60%.[1] In the Netherlands, children with AML are treated according to protocols developed by the Dutch Childhood Oncology Group (DCOG). Since 1980, four protocols for the treatment of childhood AML have been completed, and overall survival has improved from 18% to 42%.[2,3] Relapse remains the most frequent cause of treatment failure, with a cumulative risk of relapse of 30-40% in most pediatric AML studies.[1] In the consecutive Dutch AML protocols, the cumulative risk of relapse was 60, 43, 47 and 26% respectively.[3] Allogeneic stem cell transplantation (alloSCT) is generally recommended as part of treatment of relapsed AML.[4] Formal evidence for this recommendation is lacking, despite evidence of a graft-versus-leukemia effect in AML. At initial diagnosis of high-risk AML, alloSCT seems no better than chemotherapy only.[4] Therefore, the need for alloSCT in relapsed AML may be questioned, at least as a general recommendation.

We studied all Dutch children and adolescents with AML that were initially diagnosed and treated between 1980 and 1998 and relapsed before 1st January 2007. The patients were initially treated according to the Dutch Childhood Oncology Group (DCOG) protocols AML-80, AML-82, AML-87 and AML-92/94.[2,3] We focussed on patients reported to be alive without disease after treatment with chemotherapy only for their relapse and summarized the relevant literature. Since autologous SCT has been reported to provide similar results to intensive chemotherapy, and does not have a graft-versus-leukemia effect, these patients (n=9) were included in the *chemotherapy only* group.[5] Most patients were treated with a reinduction regimen containing cytarabine, most frequently in combination with an anthracycline and etoposide.

A total of 113 relapsed AML cases were identified, with a median time from first complete remission (CR1) to relapse of nine months (range 1-61 months). Ninety of these patients were treated with curative intent and CR2 was achieved in 63%. In univariate analysis, sex, age, WBC, FAB-type and SCT in CR1 were not associated with achievement of CR2. None of the patients who failed to achieve remission on first-line treatment when treated for their initially diagnosed AML (n=11) achieved CR2, compared to 72% of patients who did achieve CR1 on first-line treatment (χ^2 $p<0.0001$). CR1 duration (CR1≤1 year or CR1>1 year) correlated significantly with the probability of achieving CR2 (55 *vs.* 76%, $p=0.04$) and 10-year pOS (13 *vs.* 30%, $p=0.02$) in univariate analysis. The overall 10-year pOS was 16% (standard error (SE) 3%), with 18 disease-free long-term survivors.

AlloSCT was performed in 16 out of the 57 CR2 patients, with 8 (50%) long-term survivors. Ten out of the 41 patients (24%) treated without alloSCT survived. This comparison is biased by the fact that to be able to undergo SCT, it is necessary to have a suitable donor, to maintain CR2 until the SCT and to be in a relatively good condition. In multivariate analysis using Cox-regression, we corrected alloSCT in CR2 for time to transplant. In this analysis of pOS alloSCT was not an independent favorable prognostic factor (HR=0.56, 95% confidence interval (CI) 0.26-1.24, $p=0.15$), as was also the case for CR1 duration (HR=1.5, 95% CI 0.78-2.88, $p=0.23$). This study was limited by its retrospective nature, the diverse treatment schedules used, and the relatively small number of patients, especially when prognostic factors were analyzed. The 10 long-term survivors treated at relapse without alloSCT (7 chemotherapy only, plus 3 auto-SCT) did not have unique or similar clinical or cell biological features and included 6 patients with relapse within 12 months from CR1 (Table 1). Some of these 10 patients had been treated in the 1990s with relatively intensive chemotherapy at initial diagnosis. In 10 out of 18 survivors, late effects of treatment were reported such as

Table 1. Long-term survivors of pediatric relapsed AML after treatment with chemotherapy alone.

UPN	Relapse site	Age (yr)	Sex	FAB	Cytogenetics	Initial treatment	SCT in CR1	CR1 (m)	Relapse treatment	SCT in CR2	Events in CR2	Follow-up (m)
1	BM	14.0	f	M1	t(3;5)	DA	No	33	I: AML82 induction M: araC, dnr	Auto	No	151
2	BM	9.8	m	M3	t(15;17)	DA	No	27	I: HD araC M: araC, 6MP, vcr (5 yrs)	No	No	171
3	CNS	1.0	m	M5	Normal	I: dnr, vcr, pred M: araC, vp16, dnr, cyclo	No	9	araC i.th. 1x/wk. Continuation of M (1 yr)	No	No	176
4	BM	4.1	m	AUL	Complex	ALL, later AML80	No	7	I: DAT	No	No	183
5	BM/skin	1.2	f	M5	Unknown	AML82	No	4	I: unknown M: vp16, cyclo (2 yr)	No	No	113
6	BM/CNS	11.3	f	M4	Inv(16)	AML82	MSD	10	AML-BFM87 without M	No	No	208
7	BM	13.2	f	M5	Unknown	AML87	No	10	I: ADE, pred, cyclo	Auto	relapse: chemotherapy: CR3	
8	BM	15.8	f	M6	Unknown	AML87	No	25	araC, dox, vp16, 6TG, vcr	Auto	No	183
9	BM	4.8	m	M2au	Unknown	AML87	No	13	I: AIE, intensification HD araC and ifos. M:6TG and LD araC (4yr)	No	No	100
10	CNS	3.1	m	M5	11q23 abn	AML87	No	4	I: araC, vcr, 6MP + RT CNS, i.th. araC, pred. M: 6MP and i.th. araC, pred (3 yr)	No	No	92

UPN: unique patient number; yr: year; FAB: French-American-British; SCT: stem cell transplantation; CR1: first complete remission; CR2: second complete remission; m: months; BM: bone marrow; CNS: central nervous system; m: male; f: female; DA: daunorubicin and cytarabine; I: induction; M: maintenance; dnr: daunorubicin; vcr: vincristine; pred: prednisolon; araC: cytarabine, vp16 etoposide; cyclo: cyclophosphamide; MSD: matched sibling donor; HD: high-dose; 6MP: 6-mercaptopurine; i.th.: intrathecal; DAT: daunorubicin, cytarabine and 6-thioguanine, ADE cytarabine, daunorubicin, etoposide, dox doxorubicin, AIE cytarabine, idarubicin and etoposide, ifos ifosfamide, 6TG: 6-thioguanine; LD: low-dose; RT: radiotherapy; Auto: autologous; CR3: third complete remission.

Table 2. Reports of the outcome of children with relapsed AML.

Initial study (time period) (reference)	Time Period	Survival	Survival with chemotherapy alone
AML-BFM[6]	1987-1996	5-year pOS 21%	55% (5/9)
CCG-251/213/2861[7]	1979-1989	3-year pOS 12%*	Unknown
CCG-2891[7]	1989-1995	3-year pOS 17%*	Unknown
CCG-2951**	1997-2001	2-year pOS 24%	62% (8/13)
DCOG AML 80/82/87/9294	1980-1998	10-year pOS 16%	24% (10/41)
LAME 89/91[9]	1988-1998	5-year pOS 33%	100% (3/3)
MRC AML 10[8]	1988-1995	3-year pOS 24%	18% (3/17)
NOPHO AML 88/93[11]	1998-2003	5-year pOS 34%	44% (8/18)
St. Jude Children's Hospital AML-87/91/97[10]	1987-2002	5-year pOS 23%	0% (0/17)

*pOS: probability of overall survival. *Also included non-remitters. **Pediatric relapsed AML study .*

secondary malignancies, hypogonadotropic hypogonadism and neurological problems. Late effects were more frequently reported in children who received a SCT than in children who did not, with 9/12 patients who were treated with SCT reporting late effects, compared to 1/6 patients treated with chemotherapy alone (χ^2 p=0.019). In the literature, 6 papers describe the outcome of cohorts of pediatric relapsed AML patients (Table 2).[6-11] Overall probabilities of survival at 2-5 years ranged from 12% to 34%. Including the patients in this study, 109 relapsed pediatric AML patients treated with chemotherapy alone were reported in literature and 34 of these 91 patients were reported as survivors (31%), which is surprisingly high. However, patient selection may have occurred, and some patients may not have received optimal treatment at initial diagnosis according to current standards.

Based on these results, we question whether an alloSCT in CR2 is the only chance of cure for children with relapsed AML, as is commonly thought.[4] A randomized clinical trial to prove this has never been performed. Especially when a matched donor is unavailable, intensive chemotherapy may be preferable over a mismatched or haplo-identical donor SCT, which is associated with significant morbidity and mortality.[12,13] Currently, however, it is not known how to identify the patients who do

not need an alloSCT for cure after relapse. Results of the ongoing International BFM Study Group Pediatric Relapsed AML protocol, will contribute to this discussion in the near future. The Dutch and literature data suggest that randomized studies of the role of alloSCT in subgroups of relapsed AML are required. Meanwhile, experimental allogeneic SCT procedures, such as haplo-identical and mismatched unrelated donor SCT, should be carefully balanced against the chance of cure by chemotherapy only in patients in good quality second complete remission of AML.

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The International Prognostic Scoring System for Waldenström's macroglobulinemia is applicable in patients treated with rituximab-based regimens

Waldenström's macroglobulinemia (WM) is characterized by lymphoplasmacytic bone marrow infiltration and by production of serum monoclonal IgM.[1] This disease usually follows a relatively indolent course with a median survival ranging from 60 months to 120 months in different series. However, in some patients the disease may be more aggressive causing their death within months.[1-7] Several analyses have identified variables that may be associated with a worse prognosis. These include advanced age, cytopenia(s), hypoalbuminemia, elevated serum β2-microglobulin, high IgM, poor performance status, B-symptoms or splenomegaly.[1-8]

Recently, a multicenter collaborative project was undertaken which included a large number of previously untreated, symptomatic patients who required treatment. An International Prognostic Scoring System for WM (IPSSWM) was formulated based on 5 adverse covariates: age >65 years, hemoglobin ≥11.5 g/dL, platelet count ≤100×10^9/L, β2-microglobulin >3 mg/L and serum monoclonal protein concentration >70 g/L. Low risk is defined by the presence of ≤1 adverse variable except age, high risk by the presence of >2 adverse characteristics and intermediate risk by the presence of 2 adverse characteristics or age >65 years; 5-year survival rates are 87%, 68% and 36% respectively.[9]

However, 96% of the patients included in this analysis had received frontline treatment with alkylating agents or nucleoside analogs. Since rituximab-based regimens are now frequently used as a frontline treatment in WM patients, we analyzed whether the IPSSWM can be applied in these patients.

Ninety-three previously untreated, symptomatic patients who received treatment either with single agent rituximab (21 patients) or with the combination of dexamethasone, rituximab and cyclophosphamide (72 patients), formed the basis of this analysis. This analysis was approved by the Institutional Review Board. These patients were included in two trials reported previous-