Table 3. Comparison of patient characteristics and outcomes from authors included in the comparison conditioning regimens in allogeneic transplantation

Author (reference)	Adult/children	No. of recipients/conditioning regimen	Stage (n)	Donor	Source (n)	OS % (yr)	DFS % (yr)	TRM %
Blaize et al. (23)	Adult	50 AML/CY + TBI	CR1	MSD	BM	75 (3)	73 (3)	8
[RCT]	Adult	51 AML/BU + CY	CR1	MSD	BM	51 (3)	49 (3)	27
Ringden et al. (24)	Adult	61 AML, ALL, CML/CY + TBI	CR1 (37) CP1 (24)	MSD	BM	80 (3)	68 (3)	NR
[RCT]	Adult	58 AML, ALL, CML/BU + CY	CR1 (36) CP1 (22)	MSD	BM	83 (3)	75 (3)	NR
Neudorf et al. (19)	Children	150 AML/BU + CY	CR1	MRD	BM	67 (5)	57 (5)	17
Willemze et al. (21)	Children	55 ALL/CY + TBI	CR1	MSD	BM	74 (5)	73 (5)	6
Satwani et al. (33)	Children	29 ALL/CY + TBI	CR1	MRD	BM	58.6 (3)	58.6 (3)	3
Balduzzi et al. (34)	Children	77 ALL/TBI + etoposide, BU + CY + etoposide	CR1	MRD	BM	56.4 (5)	56.7 (5)	9.1
Bordigoni et al. (13)	Children	116 ALL/CA + MEL + TBI	CR2	MSD	BM	NR	64.8 (7)	22.4
Gordon et al. (35)	Children	27 ALL/CA + TBI	CR2	MRD	BM (26) PB (1)	NR	59 (5)	37
Bleakley et al. (36)	Children	20 ALL/CY + TBI	CR2 (17) CR3 (1) Relapse (2)	MSD	BM	60 (8)	55 (8)	20
Abrahamsson et al. (37)	Children	18 AML/NR	CR2	MRD	BM	NR	72 (5)	11

RCT, randomized controlled trial; CML, chronic myelogenous leukemia; BU, busulfan; CA, cytosine arabinoside; NR, not reported; MSD, matched sibling donor; MRD, matched related donor; BM, bone marrow; PB, peripheral blood; OS, overall survival.

Inagaki et al. (25) also reported that a conditioning regimen comprising MEL and TBI may provide sufficient antileukemic effects against advanced pediatric hematological malignancy. However, our study was a retrospective analysis of transplants performed in four centers over a relatively long time span. As selection or exclusion criteria were determined according to the decisions of individual physicians, patients in our study were not consecutive and some form of selection bias may have been present.

The rate of TRM in this study was also low, occurring in only 1 (2%) patient, and none of our patients died before engraftment, despite the high incidence of mucosal injury and febrile episodes. Helenglass et al. reported that the relapse rate after marrow transplantation is reduced in patients given TBI and MEL compared with TBI and CY (7). However, this benefit was offset by the nephrotoxicity of MEL, resulting in a high incidence of TRM (40.7%). In that study, all patients received cyclosporine (8 mg/kg/day) as GVHD prophylaxis. On the other hand, our patients received only MTX or low-dose cyclosporine (1–3 mg/kg/day) plus MTX as GVHD prophylaxis, which might have reduced the incidence of severe renal toxicities among our patients. Such a regimen combined with recent progress in supportive care might further reduce transplant mortality to $<5\%$. Five of our patients developed idiopathic interstitial pneumonitis or bronchiolitis obliterans (NCI grade ≥ 3). All these patients received only MTX as GVHD prophylaxis. Previous reports have suggested that MTX is associated with an increased risk of interstitial pneumonia (26, 27). Considering the low risk of relapse in patients who received low-dose cyclosporine and MTX, we recommend abandoning MTX alone as GVHD prophylaxis in this setting. Although Cavet et al. (28) reported two adult patients who developed constrictive pericarditis after transplantation conditioning involving MEL and TBI, our patients did not develop pericardial constriction or restrictive cardiomyopathy (28). This complication should be considered when older patients receive transplant conditioning involving MEL and TBI.

Previous reports have suggested that MEL is likely to have more carcinogenic potential than CY in non-transplant settings (29–31). One of our patients developed a secondary malignant neoplasm (osteosarcoma). Kulkarni et al. reported that the risk of developing secondary malignant neoplasms is not any higher when transplant conditioning is performed with MEL/TBI than with CY/TBI (32). Although the choice of conditioning regimen does not seem to play an important role in the development of secondary malignant neoplasms, diligent monitoring involving long-term follow-up is required.

Relapse was the most common cause of treatment failure, with 10.8% of patients in the CR1 and CR2 groups experiencing relapse, compared to 53.8% of patients with advanced-stage disease. This represents a considerable

problem to overcome among non-CR patients. Patients in non-CR may require a regimen with additional chemotherapeutic agents or immunotherapy after allo-SCT.

In conclusion, our findings suggest that the MEL/TBI regimen is a relatively well-tolerated and effective regimen before transplantation, particularly for patients in CR1 or CR2. However, the limitations of this study are the retrospective nature of the analysis and the involvement of non-consecutive patients. Further large-scale and prospective studies are thus needed to better evaluate the efficacy of this regimen.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Prognostic significance of additional cytogenetic aberrations in 733 de novo pediatric 11q23/*MLL*-rearranged AML patients: results of an international study

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We previously demonstrated that outcome of pediatric 11q23/*MLL*-rearranged AML depends on the translocation partner (TP). In this multicenter international study on 733 children with 11q23/*MLL*-rearranged AML, we further analyzed which additional cytogenetic aberrations (ACA) had prognostic significance. ACAs occurred in 344 (47%) of 733 and were associated with unfavorable outcome (5-year overall survival [OS] 47% vs 62%, $P < .001$). Trisomy 8, the most frequent specific ACA (n = 130/344, 38%), independently predicted favorable outcome within the ACAs group (OS 61% vs 39%, $P = .003$; Cox model for OS hazard ratio (HR) 0.54, $P = .03$), on the basis of reduced relapse rate (26% vs 49%, $P < .001$). Trisomy 19 (n = 37/344, 11%) independently predicted poor prognosis in ACAs cases, which was partly caused by refractory disease (remission rate 74% vs 89%, $P = .04$; OS 24% vs 50%, $P < .001$; HR 1.77, $P = .01$). Structural ACAs had independent adverse prognostic value for event-free survival (HR 1.36, $P = .01$). Complex karyotype, defined as ≥ 3 abnormalities, was present in 26% (n = 192/733) and showed worse outcome than those without complex karyotype (OS 45% vs 59%, $P = .003$) in univariate analysis only. In conclusion, like TP, specific ACAs have independent prognostic significance in pediatric 11q23/*MLL*-rearranged AML, and the mechanism underlying these prognostic differences should be studied. (*Blood*. 2011;117(26):7102-7111)

Introduction

Pediatric acute myeloid leukemia (AML) is a clinically and genetically heterogeneous disease. In addition to the patient's initial response to treatment, its prognosis is largely determined by the presence of cytogenetic abnormalities and genetic lesions.[1-6] Several recurrent cytogenetic abnormalities, such as 11q23/*MLL*-rearrangements, predict outcome in myeloid neoplasms and acute leukemia.[7] So far, > 60 different translocation partners (TPs) have been identified, and new partners are still being reported to add to the diversity of *MLL*-rearranged leukemia.[8,9] The authors of a recent international study[10] highlighted the heterogeneity of 11q23/*MLL*-rearranged pediatric AML by demonstrating that outcome is dependent on TPs. This study also revealed that additional

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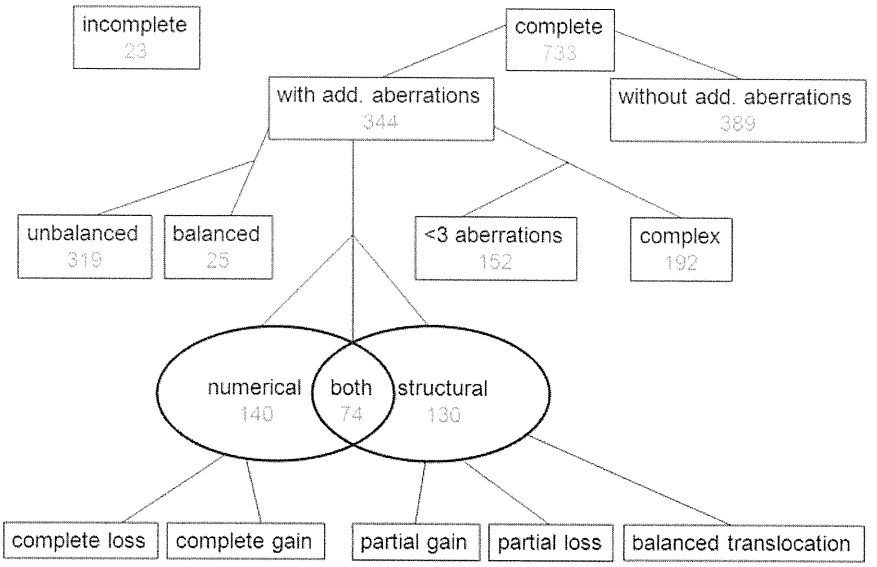

Figure 1. Flow chart showing the presence and type of ACAs in 756 pediatric patients with 11q23/MLL-rearranged AML. Complete karyotypes were not available for 23 patients, and they were therefore excluded from analyses. The presence or absence of ACAs was determined for 733 patients for whom complete karyotypes were available. In the cohort having ACAs balanced karyotype was coded for 25 patients; the remaining had an unbalanced karyotype. The types of aberrations were coded as numerical, structural, or both, and the number of aberrations was also coded. Losses and gains are further coded in other figures.

cytogenetic aberrations (ACAs) were an independent adverse prognostic factor,[10] but so far, it is unknown which additional aberration(s) determine this unfavorable outcome signature.

The authors of a recent large study in an adult AML cohort[11] showed that additional cytogenetic abnormalities in t(9;11)(p22;q23) AML did not affect outcome. However, the Berlin-Frankfurt-Münster group showed that children with t(9;11)(p22;q23) with additional aberrations had lower rates of overall survival (OS) than those with other subgroups of AML.[6]

To date, no large studies have been undertaken to study the prognostic relevance of specific ACAs in pediatric *MLL*-rearranged AML. In this multicenter international study, we retrospectively analyzed data from a large cohort (n = 733) to determine which ACAs contribute to the prognostic effect in pediatric *MLL*-rearranged AML.

Patients and methods

Patients

Patients' data collected in the retrospective international study by Balgobind et al[10] were included in this study. In summary, data from 756 patients with 11q23/*MLL*-rearranged pediatric AML were collected from 11 collaborative study groups—the Berlin-Frankfurt-Münster Study Group (Germany and Austria); the Japanese Pediatric Leukemia/Lymphoma Study Group (Japan); the Leucémies Aiguës Myéloblastiques de l'Enfant Cooperative Group (France); the Czech Pediatric Hematology Working Group (Czech Republic); the St Jude Children's Research Hospital (United States); the Associazione Italiana Ematologia Oncologia Pediatrica (Italy); Research Center for Pediatric Oncology and Hematology (Belarus); the Children's Oncology Group (United States); the Nordic Society for Pediatric Hematology and Oncology (Denmark, Finland, Iceland, Norway, and Sweden); the Dutch Children's Oncology Group (The Netherlands); and 2 centers of the Medical Research Council (United Kingdom). Patients were treated by national/collaborative group AML trials.[12-22] The treatment protocols were approved according to local law and guidelines and by the institutional review boards of each participating center, with informed consent obtained from the patients' parents or legal guardians in accordance with the Declaration of Helsinki.

Inclusion criteria for the current analyses were diagnosis between January 1, 1993, and January 1, 2005; younger than 18 years of age at diagnosis; and involvement of 11q23 or *MLL* as determined by G-, Q-, or R-banded karyotyping; FISH; or RT-PCR. Exclusion criteria were secondary AML after congenital BM failure disorders, aplastic anemia, previous chemotherapy or radiotherapy for other diseases, and previous myelodysplastic syndrome (MDS). Patients with Down syndrome were included if they met the other inclusion criteria. All clinical data obtained at initial diagnosis, data on treatment (therapy protocol, including HSCT), and all events during follow-up were checked for consistency and completeness.[10]

Cytogenetic analysis

All karyotypes were centrally reviewed by 2 cytogeneticists (J.H., S.C.R.) and assigned to 11q23/*MLL*-rearranged groups on the basis of TP.[10] All karyotypes were designated according to the International System for Human Cytogenetic Nomenclature 2005.[23]

To analyze ACAs, data from all patients with incomplete karyotypes were excluded. For all cases included in the analysis, the number of aberrations was counted. Each aberration separated from the rest of the karyotype by a comma was counted as one abnormality (regardless of its complexity), every aberration was counted only once (if present in multiple clones), and constitutional aberrations were excluded. Triploidy and tetraploidy were counted as 1 aberration (1 event). In this cohort of 11q23/*MLL*-rearranged cases, ACAs cases were defined as having 2 or more aberrations, including the 11q23/*MLL*-rearrangement (n = 344). All cases with 3 or more aberrations were considered having a complex karyotype, consistent with previously used definitions.[24,25] Numerical aberrations were defined as loss or gain of a full chromosome. Balanced translocations were defined as translocations in which no material seemed to be gained or lost as determined by conventional karyotyping. Structural aberrations were defined as aberrations resulting from breakpoints within a chromosome. In all unbalanced translocations we described which material was lost and gained and also whether 11q23 was involved. The presence of a balanced overall karyotype was defined as a karyotype with 2 complete copies of all autosomes and complete copies of sex chromosomes without any additional material (2n). Definitions used for cytogenetic classification are summarized in supplemental Table 1 (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

Statistical analyses

Complete remission (CR) was defined as < 5% blasts in the BM, with regeneration of trilineage hematopoiesis plus absence of extramedullary disease.[26] Early death was defined as any death within the first 6 weeks of treatment. Treatment of patients who did not obtain CR within the specified time in the protocol was considered a failure on day 0. OS was measured from the date of diagnosis to the date of last follow-up or death from any

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Table 1. Distribution of ACAs by translocation partner and clinically relevant parameters

			ACAs type		
	n	ACAs, n (%)	Numerical, n (%)	Structural, n (%)	Both, n (%)
TP group					
9p22	316	148 (47)	84 (57)*	40 (27)*	24 (16)*
10p12	96	48 (50)	13 (27)*	26 (54)*	9 (19)*
6q27	35	17 (49)	8 (47)*	7 (41)*	2 (12)*
19p13	30	10 (33)	6 (60)*	1 (10)*	3 (30)*
19p13.1	34	13 (38)	5 (38)*	4 (31)*	4 (31)*
19p13.3	25	13 (52)	5 (38)*	4 (31)*	4 (31)*
1q21	24	6 (25)	2 (33)*	3 (50)*	1 (17)*
4q21	13	8 (62)	2 (25)*	4 (50)*	2 (25)*
10p11.2	12	7 (58)	0*	5 (71)*	2 (29)*
17q21	12	3 (25)	1 (33)*	1 (33)*	1 (33)*
other	136	71 (52)	14 (20)*	35 (49)*	22 (31)*
	733				
Sex					
Male	358	171 (48)	78 (46)	63 (37)	30 (18)
Female	375	173 (46)	62 (36)	67 (39)	44 (25)
	733				
Age, y					
< 2	344	143 (42)	45 (31)†	68 (48)†	30 (21)†
2-9	219	115 (53)	57 (50)†	35 (30)†	23 (20)†
≥ 10	170	86 (51)	38 (44)†	27 (31)†	21 (24)†
	733				
WBC, $\times 10^9$/L					
< 20	339	175 (52)	84 (49)†	51 (29)†	40 (23)†
20-99	203	87 (43)	28 (32)†	40 (46)†	19 (22)†
≥ 100	171	73 (43)	25 (34)†	35 (48)†	13 (18)†
	713				
FAB					
M0	23	12 (52)	6 (50)	3 (25)	3 (25)
M1	39	20 (51)	9 (45)	7 (35)	4 (20)
M2	32	12 (38)	7 (58)	4 (33)	1 (8)
M4	134	49 (37)	21 (43)	21 (43)	7 (14)
M5	446	217 (49)	88 (41)	83 (38)	46 (21)
M7	19	15 (79)	7 (47)	2 (13)	6 (4)
n.d.	7	5 (71)	0	2 (40)	3 (60)
	700				
Overall		344 (47)	140 (41)	130 (38)	74 (22)

ACAs (%) indicates number of cases with additional aberrations and percentage within this group; Numerical (%), number of cases with only numerical additional aberrations and percentage of specific group (row); Structural (%), number of cases with only structural additional aberrations and percentage of specific group (row); Both (%), number of cases with both numerical and structural additional aberrations and percentage of specific group (row); and TP group, site of translocation on partner chromosome

ACA indicates additional cytogenetic aberrations; dx, diagnosis; FAB, French American British morphology classification subtype; n.d., not determined; TP, translocation partner; and WBC, white blood cell count.

*Values significantly different at the $P < .01$ level (χ^2).

†Values significantly different at the †$P < .05$ level (χ^2).

cause. Event-free survival (EFS) was calculated from the date of diagnosis to the first event or to the date of last follow-up. Events included nonremittance, relapse, secondary malignancy, or death from any cause. Cumulative incidence of relapse (CIR) was calculated from the date of CR to the first relapse. Refractory disease was included in the EFS and CIR analyses by arbitrarily setting the event date on day 0. For OS, EFS, and CIR analyses, patients who did not experience an event were censored at the time of last follow-up.

The Kaplan-Meier method was used to estimate the 5-year probabilities of OS and EFS, and survival estimates were compared by the log-rank test. The Gray test for competing risks was used for CIR analysis. Multivariate analyses were performed with the Cox proportional hazards model. Continuous variables known to be of prognostic value in AML were categorized according to cutoff points (eg, > 2 or 10 years of age, white blood cell [WBC] count $< 20 \times 10^9$/L or $> 100 \times 10^9$/L]). The χ^2 or Fisher exact test was used to compare differences in proportions of variables among groups; the Mann-Whitney *U* test was used for continuous variables. All *P* values are descriptive and explorative and were considered significant if ≤ .05. All statistical data were analyzed by the use of SAS-PC, Version 9.1 (SAS Institute Inc).

Results

Distribution of ACAs

Of the 756 patients, 733 (97%) had complete karyotypes, and their data were included in the study (see flowchart in Figure 1). There were no significant differences in the patients included (n = 733) and not included (n = 23) in this study with respect to sex, age, WBC count, and TP group (data not shown). ACAs were found in 344 (47%) of 733 cases (Figure 1). The number of additional aberrations ranged from 0 to 15 (mean, 1.2 additional aberrations; supplemental Figure 1).

There were 3 or more aberrations (including the 11q23/*MLL*-rearrangement) in 192 of 733 (26%) cases, which were therefore

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Table 2. Number of aberrations by 11q23 translocation partner and clinically relevant parameters

	Number of aberrations							
	0	1	2	3	4	5	> 5	All
TP group								
9p22		168 (44)*	75 (49)*	33 (41)*	19 (43)*	7 (28)*	14 (33)*	316 (43)
10p12	1 (14)*	47 (12)*	19 (13)*	12 (15)*	7 (16)*	5 (20)*	5 (12)*	96 (13)
6q27	1 (14)*	17 (4)*	7 (5)*	1 (1)*			9 (21)*	35 (5)
19p13		20 (5)*	3 (2)*	4 (5)*	1 (2)*	1 (4)*	1 (2)*	30 (4)
19p13.1	1 (14)*	20 (5)*	7 (5)*	2 (3)*	1 (2)*	3 (12)*		34 (5)
19p13.3		12 (3)*	7 (5)*		3 (7)*	2 (8)*	1 (2)*	25 (3)
1q21		18 (5)*	3 (2)*	1 (1)*	1 (2)*		1 (2)*	24 (3)
4q21		5 (1)*	2 (1)*	4 (5)*	1 (2)*	1 (4)*		13 (2)
10p11.2		5 (1)*	2 (1)*	3 (4)*		2 (8)*		12 (2)
17q21		9 (2)*	1 (1)*	1 (1)*			1 (2)*	12 (2)
Other	4 (57)*	61 (16)*	26 (17)*	19 (24)*	11 (25)*	4 (16)*	11 (26)*	136 (19)
								733
Sex								
Male		187 (49)†	89 (59)†	35 (44)†	13 (30)†	11 (44)†	23 (53)†	358 (49)
Female	7 (100)†	195 (51)†	63 (41)†	45 (56)†	31 (70)†	14 (56)†	20 (47)†	375 (51)
								733
Age, y								
< 2	4 (57)*	197 (52)*	61 (40)*	39 (49)*	12 (27)*	16 (64)*	15 (35)*	344 (47)
2-9		104 (27)*	49 (32)*	29 (36)*	22 (50)*	5 (20)*	10 (23)*	219 (30)
≥ 10	3 (43)*	81 (21)*	42 (28)*	12 (15)*	10 (23)*	4 (16)*	18 (42)*	170 (23)
								733
WBC, $\times 10^9$/L								
< 20	5 (71)	159 (42)	76 (50)	39 (49)	23 (52)	16 (64)	21 (49)	339 (46)
20-99	1 (14)	115 (30)	38 (25)	20 (25)	14 (32)	5 (20)	10 (23)	203 (28)
≥ 100	1 (14)	97 (25)	34 (22)	19 (24)	7 (16)	2 (8)	11 (26)	171 (23)
								713 (97)
FAB								
M0		11 (3)*	4 (3)*	2 (3)*	3 (7)*	1 (4)*	2 (5)*	23 (3)
M1		19 (5)*	12 (8)*	4 (5)*	1 (2)*		3 (7)*	39 (5)
M2	1 (14)*	19 (5)*	7 (5)*	2 (3)*	3 (7)*			32 (4)
M4	2 (29)*	83 (22)*	25 (16)*	12 (15)*	5 (11)*	2 (6)*	5 (12)*	134 (18)
M5	4 (57)*	225 (59)*	97 (64)*	54 (68)*	24 (55)*	17 (68)*	25 (58)*	446 (61)
M7		4 (1)*	3 (2)*	2 (3)*	4 (9)*		6 (14)*	19 (3)
n.d.		2 (1)*	1 (1)*	1 (1)*	1 (2)*	1 (4)*	1 (2)*	7 (1)
								700 (95)
Overall	7 (1)	382 (52)	152 (21)	80 (11)	44 (6)	25 (3)	43 (6)	733

The number of aberrations indicates total number of aberrations in the karyotype, including 11q23/MLL-rearrangement, percentages per group shown in parentheses (per column).

dx indicates diagnosis; FAB, French American British morphology classification subtype; n.d., not determined; TP, translocation partner; and WBC, white blood cell count.

*Significantly different at the $P < .01$ level (χ^2).

†Significantly different at the $P < .05$ level (χ^2).

defined as complex karyotypes. Of the 344 cases with ACAs, 140 (41%) had numerical ACAs only, 130 (38%) had structural ACAs only, and 74 (22%) had both numerical and structural ACAs (Figure 1). There were 25 (7%) cases of ACA that had only balanced structural abnormalities in their karyotypes (Figure 1).

Distribution of ACAs in clinically relevant groups

Tables 1 and 2 show the distribution of ACAs by TP group and clinically relevant parameters (sex, age, WBC count, and FAB [ie, French-American-British] subtype). TP groups 9p22 and 19p13 were characterized by a relatively high frequency of numerical ACAs, whereas groups 10p12, 10p11.2, and 4q21 showed greater prevalence of structural ACAs ($P < .001$; Table 1). Also, there were significant differences in the number of aberrations among TP groups: the 6q27 group had a relatively high number of ACAs ($P = .002$), whereas groups 9p22, 19p13, and 1q21 had a lower number of ACAs (Table 2).

ACAs were less likely to occur in young children (< 2 years of age) than in children 2-9 years of age or 10 years or older (42% vs 53% vs 51%, $P = .02$; Table 1). However, structural ACAs were more frequent in children < 2 years of age than in children 2-9 years of age or 10-18 years of age (48% vs 30% vs 31%, $P < .01$; Table 1). There was a greater prevalence of highly complex karyotypes (> 5 aberrations) in children 10-18 years of age than those younger than 2 years or 2-9 years of age (11% vs 4% vs 5%, $P = .02$, Table 2).

Although the number of patients with FAB M7 was small, ACAs were more likely to occur in patients with AML FAB M7 compared with those with other FAB types (79% vs 46%, $P = .008$), whereas patients with AML FAB M2 and M4 had the lowest occurrence of ACAs (Table 1). Also, patients with AML FAB M7 seem to have a higher number of aberrations than those with other FAB morphologies ($P = .003$; Table 2).

Specific recurrent aberrations

Trisomy 8 was the most frequently occurring numerical abnormality (130/733, 18% of all cases and 38% of ACA cases, Figure 2A). In addition, trisomy 4, 6, 13, 19, and 21 were recurrent ACAs (at least 15 cases each). Two cases with Down syndrome were included in this study. However, because constitutional aberrations

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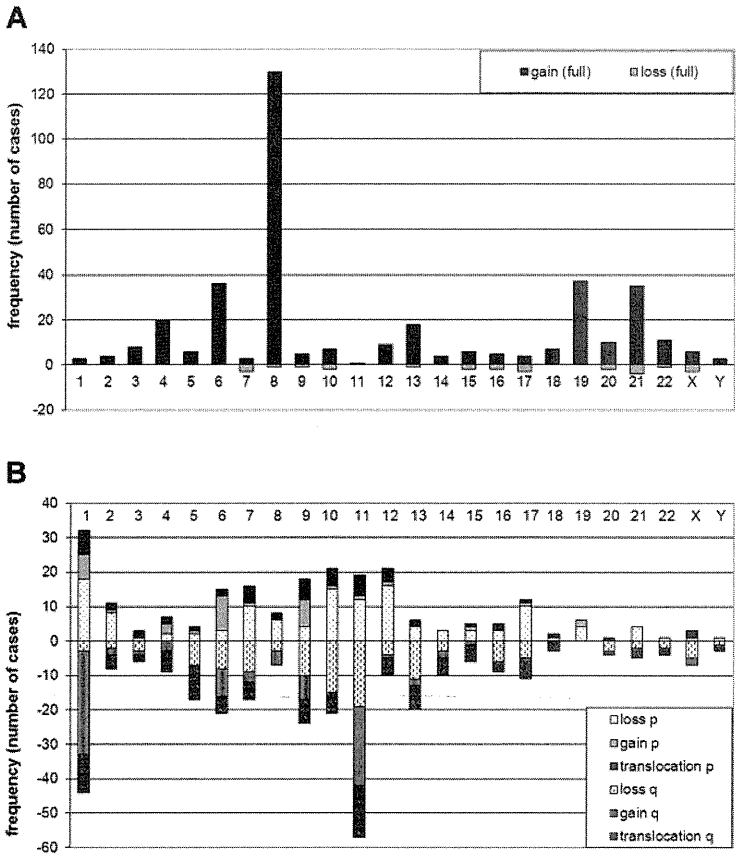

Figure 2. Frequency (number of cases) of numerical and structural ACAs. (A) Numerical ACAs. Gains are shown on the positive y-axis, and losses are shown on the negative y-axis. Chromosomes are on the x-axis. (B) Structural ACAs The short arms (p) of the chromosomes are shown on the positive y-axis and the long arms (q) on the negative y-axis. Lightest shades are used for losses, medium-shaded colors are used for gains, and the darkest-shaded colors for breakpoints of balanced translocations. Chromosomes are on the x-axis. Balanced 11q23 translocations are not included in the figure.

were not included in the additional aberrations, they were not included in the trisomy 21 group. Only 11 patients had losses of full chromosomes, collectively accounting for 25 monosomies (Figure 2A).

Figure 2B shows the collective analysis of structural ACAs per chromosome arm but does not include breakpoints involved in balanced 11q23/*MLL*-translocations. However, the figure includes unbalanced 11q23/*MLL*-translocations in which chromosomal

Table 3. Univariate survival analysis of the complete cohort (n = 733)

	Complete cohort						
	n	EFS	*P* (log-rank)	OS	*P* (log-rank)	CIR	*P* (Gray)
Additional aberrations			.002†		< .001†		< .001†
Absent	389	0.48		0.62		0.38	
Present	344	0.38		0.47		0.52	
No. of aberrations			< .001†		< .001†		.001†
2	152	0.39		0.50		0.50	
3	80	0.45		0.53		0.48	
≥ 3	192	0.37	.018*	0.45	.003†	0.53	< .001†
4	44	0.40		0.50		0.53	
5	25	0.36		0.43		0.60	
> 5	43	0.18	< .001†	0.25		0.61	
Type			.001†		.003†		< .001†
Numerical	140	0.47		0.56		0.41	
Structural	130	0.32		0.43		0.59	
Both	74	0.31		0.40		0.59	
Trisomy							
4	20	0.43	.72	0.52	.87	0.52	.93
6	36	0.35	.43	0.35	.029*	0.54	.65
8	130	0.53	< .001†	0.61	.003†	0.35	< .001†
13	18	0.49	.52	0.64	.41	0.40	.37
19	37	0.17	.003†	0.24	< .001†	0.54	.88
21	35	0.19	.007†	0.28	.015*	0.69	.014*

CIR, indicates 5-year cumulative incidence of relapse; EFS, 5-year event-free survival estimates; n, number of patients; OS, 5-year overall survival estimate; *P* (Gray), *P* value from the Gray test; and *P* (log-rank), *P* value from log-rank test.

*Significant at $P < .05$ level.

†Significant at $P < .01$ level.

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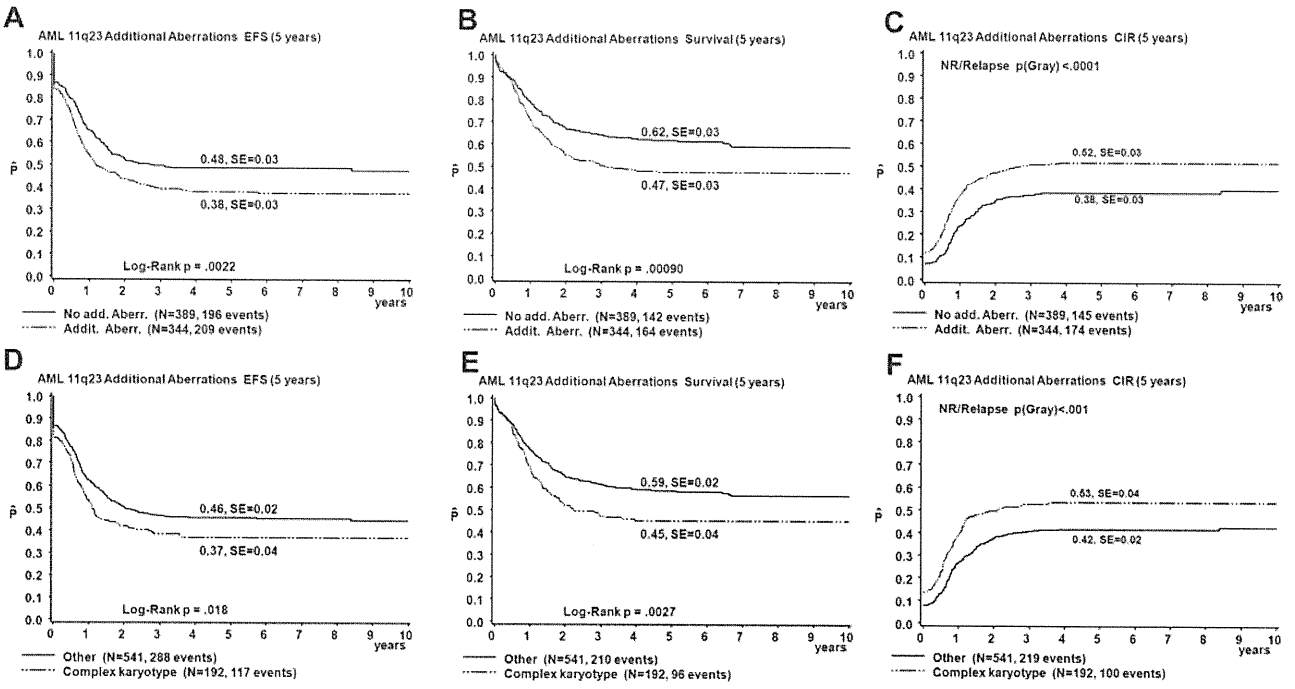

Figure 3. Survival curves obtained from univariate analysis comparing patients with ACAs to patients without ACAs and comparing patients with complex karyotype with all patients with < 3 aberrations. (A-C) Patients with ACAs are compared to patients without ACAs. (D-F) Patients with complex karyotype are compared to patients with < 3 aberrations. EFS (A,D), OS (Survival; B,E), and CIR (C,F).

material was lost or gained. Chromosomes 1 and 11 were most frequently involved in structural ACAs. Analysis of specific breakpoints showed that 11q23 was the only breakpoint found more than 10 times (data not shown).

Univariate analysis of the prognostic impact of ACAs on survival

Table 3 summarizes results of the univariate analysis of survival parameters. The EFS and OS estimates of patients with ACAs were significantly lower than those without ACAs (EFS 38% vs 48%, $P = .002$; OS 47% vs 62%, $P < .001$; Figure 3). CIR estimates of patients with ACAs were significantly greater than for those without ACAs (52% vs 38%, $P < .001$; Figure 3). Patients with complex karyotypes had significantly worse outcomes than those without complex karyotypes (EFS 37% vs 46%, $P = .02$; OS 45% vs 59%, $P = .003$; CIR 53% vs 42%, $P < .001$; Figure 3).

The presence of trisomy 8 (n = 130) was a favorable prognostic factor (EFS 53% vs 29% for patients without trisomy 8, $P < .001$; OS 61% vs 39% for patients without trisomy 8, $P = .003$; CIR 35% vs 62% for patients without trisomy 8, $P < .001$; Figure 4). Survival differences are mainly explained by reduced relapse rate in trisomy 8 patients (relapse rate 26% vs 49% for patients without trisomy 8, $P < .001$; Figure 4). The presence of trisomy 19 (n = 37) and trisomy 21 (n = 36) was an unfavorable prognostic factor (EFS 17% vs 40% for patients without trisomy 19, $P = .003$; OS 24% vs 50% for patients without trisomy 19, $P < .001$; CIR 54% vs 51% for patients without trisomy 19, $P = .88$; and EFS 19% vs 40% for patients without trisomy 21, $P = .007$; OS 28% vs 50% for patients without trisomy 21, $P = .02$; CIR 69% vs 50% for patients without trisomy 21, $P = .01$; Figure 4). Both trisomies 19 and 21 were present in 15 patients. Survival curves for patients with either trisomy 19 or 21 were not different from those for patients with both trisomies 19 and 21 (Figure 4). Combined trisomy 19 and trisomy 8 was present in 23 patients. These patients showed a survival curve intermediate to that of trisomy 8 and trisomy 19 cases (EFS 30%, data not shown). The survival disadvantage of patients with trisomy 19 seems to be determined by refractory disease (probability of CR 74% for patients with trisomy 19 vs 89% for patients with other ACAs, as calculated over the fraction of patients who survive beyond the first 6 weeks after diagnosis, $P = .04$) rather than relapse. In addition, patients with trisomy 19 had a significantly greater incidence of early death (16% vs 3.3% in other ACA cases, $P = .004$), which could not be explained by adverse clinical prognostic factors such as greater WBC or age. Structural aberrations were diverse and randomly distributed among TP groups and survival analysis of patients with specific breakpoints was not feasible because none of the breakpoints was involved > 10 times.

Multivariate analyses of the prognostic impact of ACAs on survival

Table 4 summarizes results of the multivariate survival analysis. Cox proportional hazards model for EFS, OS, and relapse incidence of the full cohort (n = 733) showed that trisomy 8 and trisomy 19 were independent prognostic factors at $P < .05$ for EFS (hazard ratio [HR] 0.57, $P = .02$; and HR 1.77, $P = .01$) and OS (HR 0.54, $P = .03$; and HR 2.11, $P = .002$; Table 4). Structural aberrations as a general finding predicted EFS (HR 1.39, $P = .01$; Table 4). The TPs identified by Balgobind et al[10] (10p12, 6q27, 1q21, and 10p11.2) remained significant independent prognostic factors in these models. Trisomy 8, 19, and 21 were not significant factors in the model for the prediction of relapse incidence. Complexity of the karyotype, tested by different cutoff values (≥ 2 aberrations, ≥ 3 aberrations, and > 5 aberrations), was not a significant factor for outcome in all models and was therefore excluded from the final model. A separate analysis of t(9;11)(p22;q23) cases showed that they did not differ considerably from the complete cohort (supplemental Figure 2 and supplemental Table 2).

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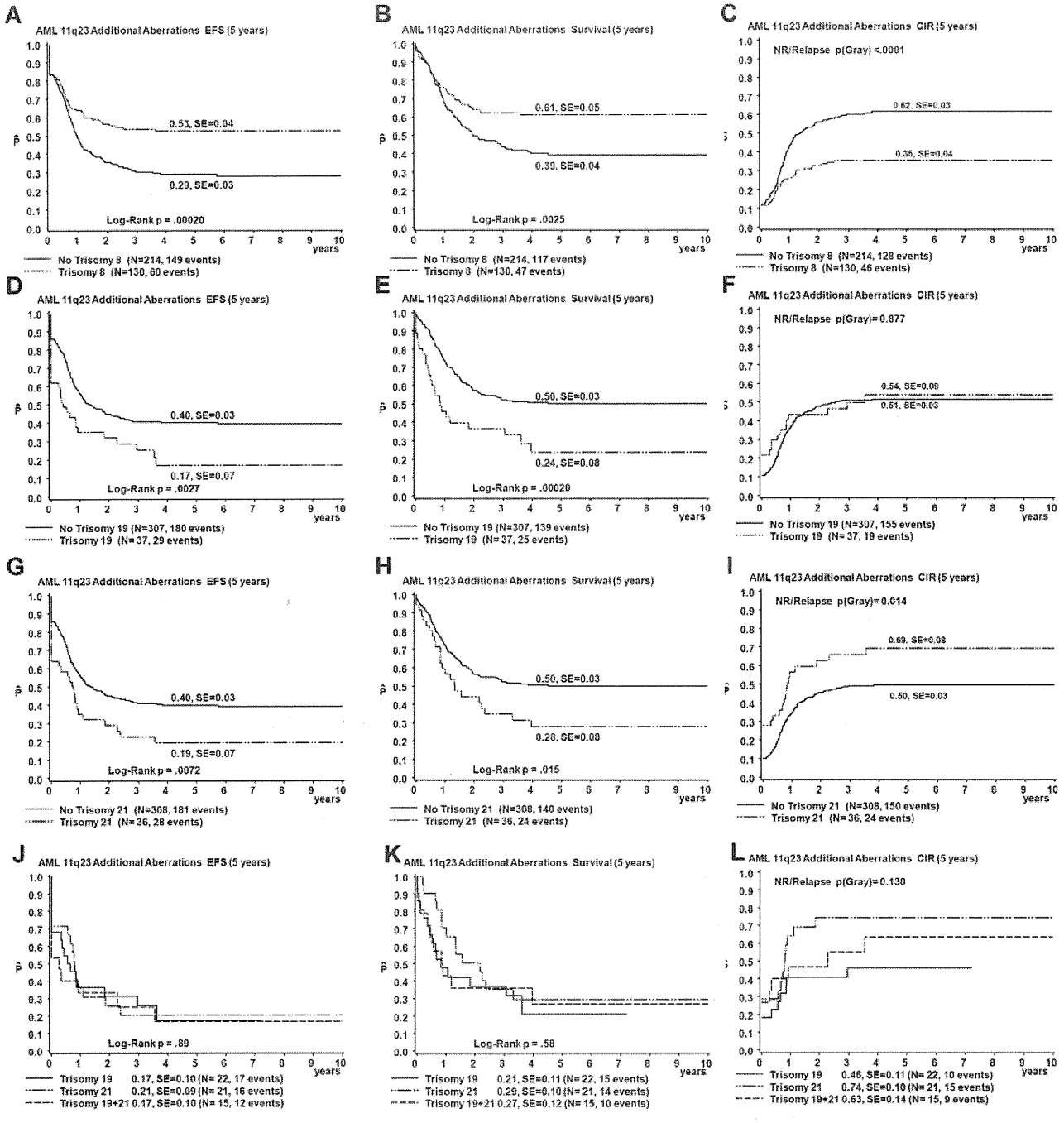

Figure 4. Comparison of survival curves obtained from univariate analysis for patients with trisomy 8, trisomy 19, and those with trisomy 21 and defined by strata of occurrence of trisomy 19 and trisomy 21. For curves A-I, patients with a specific trisomy are compared with patients with other ACAs. Patients with trisomy 8 are shown in parels A-C, patients with trisomy 19 in panels D-F, and patients with trisomy 21 in panels G-I. The strata of occurrence of trisomy 19 and trisomy 21 are shown in panels J-L. EFS (A,D,G,J), OS (Survival; B,E,H,K), and CIR (C,F,I,L).

Discussion

The heterogeneity of pediatric AML is mainly determined by specific karyotypes and molecular aberrations, which have become important prognosticators.[1,3-6,8,11,27-33] In addition, within distinct groups such as 11q23/*MLL*-rearranged AML, we have reported that additional cytogenetic aberrations are of prognostic relevance.[10] In the present exploratory study, we identified trisomy 8, trisomy 19, and trisomy 21 to be recurrent ACAs of prognostic significance in pediatric 11q23/*MLL*-rearranged AML. Multivariate analysis showed that only trisomy 8 and trisomy 19 as additional aberrations were of independent prognostic value. Notably, the adverse outcome for 11q23/MLL-rearranged AML patients harboring trisomy 19 was because of refractory disease and early death rather than an increased rate of relapse. Complex karyotype was a frequent finding (26%) and a negative prognostic factor in univariate analysis only.

Trisomy 19 in AML is an aberration that is rarely found as the sole aberration.[34] In infants with AML it is associated with t(7;12)(q36;p13) and t(7;12)(q32;p13).[35] In most of such cases it can seem to be the sole aberration because of the cryptic t(7;12).[35]

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Table 4. Multivariate survival analysis of the complete cohort by use of the Cox proportional hazards model

	Cox proportional hazards model								
	EFS			OS			Relapse incidence		
	HR	CI	*P*	HR	CI	*P*	HR	CI	*P*
TP									
9p22	1	reference		1	reference		1	reference	
other	1.15	(0.87-1.51)	.328	1.13	(0.82-1.57)	.461	1.17	(0.92-1.47)	.195
10p12	1.36	(1.01-1.83)	.042*	1.62	(1.16-2.27)	.005†	1.76	(1.36-2.29)	.000†
6q27	2.29	(1.54-3.39)	.000†	2.72	(1.77-4.19)	.000†	2.79	(1.80-4.33)	.000†
19p13	1.06	(0.62-1.80)	.832	1.44	(0.82-2.51)	.204	0.88	(0.57-1.37)	.579
19p13.1	1.11	(0.69-1.79)	.667	0.97	(0.53-1.77)	.931	1.04	(0.71-1.53)	.841
19p13.3	1.06	(0.60-1.88)	.832	1.64	(0.90-3.00)	.105	1.18	(0.71-1.94)	.522
1q21	0.12	(0.03-0.49)	.003†	0.00			0.68	(0.44-1.05)	.080
4q21	1.46	(0.74-2.88)	.276	2.04	(1.02-4.09)	.043*	1.84	(0.99-3.43)	.054
10p11.2	2.12	(1.10-4.06)	.024*	2.56	(1.24-5.32)	.011*	1.37	(0.67-2.78)	.384
17q21	1.14	(0.53-2.43)	.743	1.15	(0.47-2.82)	.763	1.28	(0.68-2.42)	.446
Trisomy									
No trisomy	1	reference		1	reference		1	reference	
8	0.57	(0.36-0.92)	.022*	0.54	(0.32-0.94)	.028*	0.79	(0.56-1.12)	.188
19	1.77	(1.13-2.78)	.012*	2.11	(1.31-3.42)	.002†	1.15	(0.68-1.94)	.596
21	1.35	(0.85-2.13)	.198	1.25	(0.76-2.03)	.377	0.98	(0.60-1.60)	.926
Type									
No ACAs	1	reference		1	reference		1	reference	
numerical	1.16	(0.83-1.63)	.376	1.17	(0.84-1.62)	.353	1.09	(0.81-1.47)	.588
structural	1.39	(1.07-1.80)	.013*	1.27	(0.98-1.63)	.068	1.13	(0.90-1.43)	.288

Results are of 3 independent analyses.
ACA indicates additional cytogenetic aberrations; CI, 95% confidence interval; EFS, event-free survival; HR, hazard ratio; and OS, overall survival.
*Significant at $P < .05$ level.
†Significant at $P < .01$ level.

Trisomy 19 has been described as an additional aberration with adverse prognostic significance in adult AML.[11] It has been postulated that a gene dosage effect of the DNA methyltransferase 1 located on 19p13.2 contributes to the hypermethylation found in patients with MDS and thereby to prognosis.[36] Future studies may reveal whether this mechanism also contributes to aberrant methylation found in pediatric 11q23/*MLL*-rearranged AML.[37]

In our study, trisomy 8 was found to be an independent favorable prognostic factor. Kok et al[38] identified a gene expression signature with high *HOX*A gene expression in adult AML patients with AML with trisomy 8 as the sole abnormality, which clustered together with patents with *MLL*-rearranged AML. This finding may suggest similarities in the biology of these diseases. In contrast, in pediatric MDS, trisomy 8 is recognized as a positive prognostic factor, possibly because of differences in apoptosis regulation between cells with trisomy 8 and cells with other abnormalities.[39,40] To date, it is not clear how trisomy 8 influences the biology of *MLL*-rearranged AML.

Interestingly, in our study, although 26% of all cases of 11q23/*MLL*-rearranged had complex karyotypes, this ACA was not an independent prognostic factor. Although the use of definitions on complex karyotypes is not uniform, the occurrence of complex karyotypes in pediatric AML cohorts has been reported to range from 7% to 15%.[2,6,14,41] A Cancer and Leukemia Group B study on adult de novo AML showed that patients with increased number of aberrations had significantly worse outcome than those with normal karyotypes.[42] Recently, Göhring et al[43] used a new definition of "structural complex karyotype," defined as a karyotype with ≥ 3 chromosomal aberrations including at least one structural aberration. This specific karyotype independently predicted very poor survival in a cohort of 192 children with advanced MDS.[43]

Although all the cases of complex karyotype in our study fit their definition, we did not find the presence of such karyotype to be associated with the poor prognosis that was reported in pediatric advanced MDS.[43] Only some studies have specifically shown a correlation between complexity of the karyotype and outcome in pediatric AML.[2,6,14,33,44] EFS rates for patients with complex karyotype have ranged from 29% to 42% in these studies, which is comparable with the EFS obtained in our study. Alternatively, a strong negative association between monosomal karyotype, defined as a karyotype with at least 2 monosomies or 1 monosomy combined with at least 1 structural aberration, and outcome was described in adult AML.[45] This monosomal karyotype was only present in 1.5% (n = 11) of our cases and therefore it was not possible to evaluate the predictive value in our pediatric 11q23/*MLL*-rearranged AML cohort.

Although we have added additional prognostic factors in our study, the multivariate models still point out that previously determined risk factors (among which the TPs) retain their independent prognostic significance irrespective of ACA status.

A limitation of our study is the variety of treatment regimens, although all protocols had a similar backbone, including intensive chemotherapy with cytarabine/anthracycline. Unfortunately, numbers were too small to do specific analyses for different protocols, or to draw any meaningful conclusion regarding provided treatment and outcome.

In separate analysis of t(9;11)(p22;q23) cases, we confirmed most of the findings from the complete cohort, regarding frequent recurrent aberrations and predictive factors. In addition, FAB M5 morphology was still recognized as independent favorable prognostic factor in this group of patients.

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In conclusion, in this exploratory study we have identified specific ACAs as novel independent prognostic variables in pediatric 11q23/*MLL*-rearranged AML, which can be identified by conventional karyotyping. Future studies should be aimed to test the associations found in this study in different patient cohorts. Our findings may also guide further studies that unravel the biologic differences that determine outcome differences in 11q23/MLL-rearranged AML as well as future treatment stratification.

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Authorship

Contribution: E.A.C., S.C.R., J.H., R.P., C.M.Z., and M.M.v.d.H.-E. conveyed and planned the study, analyzed the data, and wrote the paper; M.Z. performed the statistical analyses and wrote the paper; and T.A.A., A.A., H.B.B., M.C., U.C., M.N.D., E.F., B.G., H.H., C.J.H., N.A.H., G.J.L.K., A.L., N.L., L.L.N., A.M., C.P., D.R., J.E.R., F.O.S., J.S., I.S., S.S., T.T., D.T., D.W., and Z.Z. participated in data collection and in critical review and final approval of the paper.

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Continuous and High-Dose Cytarabine Combined Chemotherapy in Children with Down Syndrome and Acute Myeloid leukemia: Report from the Japanese Children's Cancer and Leukemia Study Group (JCCLSG) AML 9805 Down Study

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Background. The aim of the JCCLSG AML 9805 Down study was to evaluate the effect of continuous and high-dose cytarabine combined chemotherapy on the survival outcome of acute myeloid leukemia (AML) with Down syndrome (DS). ***Procedure.*** From May 1998 to December 2006, DS patients with newly diagnosed AML were enrolled. Remission induction therapy consisted of two courses of pirarubicin, vincristine, and continuous-dose cytarabine (AVC1). The patients who achieved complete remission (CR) after two courses of AVC1 were subsequently treated with mitoxantrone and continuous-dose cytarabine (MC), etoposide and high-dose cytarabine (EC) and pirarubicin, vincristine, and continuous-dose cytarabine (AVC2). ***Results.*** Twenty-four patients were enrolled. All patients were younger than 4 years and diagnosed as having acute megakaryoblastic leukemia. Twenty-one patients achieved CR. Three patients died during remission induction therapy due to serious infection. No toxic deaths were observed during remission. All but one patient maintained CR without serious complications. The 5-year overall and event-free survivals were 87.5% ± 6.8% and 83.1% ± 7.7%, respectively. ***Conclusions.*** Continuous and high-dose cytarabine combined chemotherapy with reduced intensity would be effective in DS children with AML. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

Key words: AML; Clinical trials; Down syndrome

INTRODUCTION

Down syndrome (DS) is one of the most common chromosomal abnormalities and is associated with an increased risk of leukemia [1]. The clinical and biological features of acute myeloid leukemia (AML) in DS children are quite different from those in children without DS: younger age, lower white blood cell count, and high incidence of acute megakaryoblastic leukemia [2,3]. Before the 1990s, most patients with AML with DS (AML-DS) received suboptimal therapy, resulting in poor outcomes. In 1992, high rates of event-free survival (EFS) with intensive AML treatment were reported from the pediatric oncology group (POG) [4]. After recognition of the favorable outcome of AML-DS patients treated with the AML protocol, recruitment to collaborative studies for AML-DS patients increased, but it became apparent that treatment-related toxicity was high in most series [5–7]. Since then, several collaborative groups have adapted their AML protocols for AML-DS by reducing the dosage of chemotherapeutic agents [6].

We report herein the results of the Japanese Children's Cancer and Leukemia Study Group AML 9805 Down study, which evaluated the feasibility, efficacy, and safety of continuous and high-dose cytarabine combined chemotherapy, which was adapted for DS patients by reducing dose intensity.

PATIENTS AND METHODS

Patients

Between May 1998 and December 2006, 24 AML patients with DS entered the Japanese Children's Cancer and Leukemia Study Group AML 9805 Down study after informed consent was obtained. Neonates with transient myeloproliferative disorder (TMD), defined as appearance of myeloid blasts within the first months of life, and those with spontaneous remission were not included. All children and adolescents less than 18 years of age with no prior treatment were eligible. The initial diagnosis of AML and its subtypes was determined according to the FAB classification by institution pathologists, with central review for most cases.

Therapy

The scheme of treatment for the JCCLSG AML 9805 Down study is shown in Table I. Remission induction therapy consisted of two courses of AVC1 (cytarabine (Ara-C) 100 mg/m^2/day continuous infusion on days 1–7, pirarubicin 25 mg/m^2 by 60 min infusion on days 2, and 4, and vincristine (VCR) 0.7 mg/m^2 on day 7).

Patients who achieved complete remission (CR) after two courses of AVC1 were subsequently treated with MC (Ara-C 100 mg/m^2/day continuous infusion on days 1–5 and mitoxantrone (MIT) 3.5 mg/m^2 by 60 min infusion days 2–4), EC (high-dose Ara-C 1 g/m^2 every 12 hr on days 1–5, and etoposide 66 mg/m^2 by 2 h infusion on days 2–4) and AVC2 (Ara-C 100 mg/m^2/day continuous infusion on days 1–5, pirarubicin 35 mg/m^2 by 60 min infusion on day 2, and VCR 0.7 mg/m^2 on day 5).

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Conflict of Interest: Nothing to report.

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TABLE I. Treatment Regimen of the JCCLSG AML9805 Down Study

	Regimen	Administration	Daily dose	Days
Induction				
AVC1	Cytarabine	IV (24 h)	100 mg/m^2	1–7
	Pirarubicin	IV (1 h)	25 mg/m^2	2–4
	Vincristine	IV	0.7 mg/m^2	7
	Methotrexate	IT	Age-adjusted[a]	1
	Cytarabine	IT	Age-adjusted[a]	1, (5, 10)[b]
	Hydrocortisone	IT	Age-adjusted[a]	1, (5, 10)[b]
Consolidation				
MC	Cytarabine	IV (24 h)	100 mg/m^2	1–5
	Mitoxantrone	IV (1 h)	3.5 mg/m^2	2–4
EC	Cytarabine	IV (2 h)	1 g × 2 /m^2	1–5
	Etoposide	IV (2 h)	66 mg/m^2	2–4
AVC2	Cytarabine	IV (24 h)	100 mg/m^2	1–5
	Pirarubicin	IV (1 h)	35 mg/m^2	2
	Vincristine	IV	0.7 mg/m^2	5
	Methotrexate	IT	Age-adjusted[a]	1
	Cytarabine	IT	Age-adjusted[a]	1
	Hydrocortisone	IT	Age-adjusted[a]	1

Recommended interval of each cycle was 4 weeks. [a]The doses were adjusted according to patient's age as follows: younger than 1 year, methotrexate (MTX) 5 mg, cytarabine (Ara-C) 10 mg, hydrocortisone (HDC) 10 mg; younger than 2 years, MTX 8 mg, Ara-C 20 mg, HDC 15 mg; younger than 3 years, MTX 10 mg, Ara-C 30 mg, HDC 20 mg; 3 years and older, MTX 12 mg, Ara-C 40 mg, HDC 25 mg. [b]For CNS-positive patients. The doses were adjusted according to patient's age as follows: younger than 1 year, cytarabine (Ara-C) 20 mg, hydrocortisone (HDC) 10 mg; younger than 2 years, Ara-C 30 mg, HDC 15 mg; younger than 3 years old, Ara-C 50 mg, HDC 20 mg; 3 years and older, Ara-C 70 mg, HDC 25 mg.

Prophylactic treatment for central nervous system (CNS) leukemia was performed by intrathecal injection of Ara-C, methotrexate, and hydrocortisone on the first day of AVC1 and AVC2. An absolute neutrophil count of more than 1,500/μL and a platelet count of more than 75,000/μL were the criteria for starting the first course of consolidation therapy, and an absolute neutrophil count of more than 1,500/μL and a platelet count of more than 100,000/μL were the criteria for starting the second course.

Definitions and Statistics

Evaluation of each treatment was performed on the 28th day. Treatment response was defined as follows: CR, less than 5% blasts in the bone marrow; partial remission (PR), less than 15% blasts; and no response (NR), more than 15% blasts or progressive disease at other sites.

CNS involvement was diagnosed if more than 5 leukocytes/μL were identified in the cerebrospinal fluid (CSF) in combination with detectable leukemic cells in the cytospin and/or with neurological symptoms (e.g., cranial nerve palsy).

EFS was calculated from the date of the first day of chemotherapy to last follow-up or to the first event (early death, resistant leukemia, relapse, or death from any cause). The EFS time of patients with an induction failure was calculated as zero. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.

Univariate comparisons of the survival data were performed using the log-rank test. The Statistical Analysis Software (SAS) computer program was used for the analysis. Follow-up data were actualized as of July 31, 2009.

RESULTS

Patient Characteristics

The relevant initial clinical and hematological data of the 24 patients in this study are shown in Table II. Males predominated, and all patients were younger than 4 years (median age, 17 months). The median white blood cell count was 6,500/μL (range 500–70,900/μL). All patients showed FAB M7 morphologically. No patients had CNS involvement. One patient had an extramedullary mass (skin) at initial diagnosis. Cytogenetic analysis of leukemic blasts was available for 22 patients. Favorable cytogenetics, such as inv (16) and t (8; 21), were not observed. Six patients had normal karyotypes with constitutional trisomy 21 only. The remainder had complex karyotypes with aneuploidy and translocation. GATA1 mutation was confirmed only in one patient.

Seven patients had a history of TMD. No patients of them received cytarabine therapy. Nine patients had documented congenital heart disease. Most patients had either surgically repaired defects or asymptomatic atrial septal defect or ventricular septal defect with normal function.

Overall Outcome

Overall, 21 (87.5%) of 24 patients achieved first remission. One patient relapsed with an isolated extramedullary mass after cessation of chemotherapy. The patient has been in third remission after chemotherapy, electron beam irradiation and cord blood cell transplantation following reduced intensity conditioning. The other 20 patients remain in first CR. Estimated 5-year OS and EFS were 87.5% ± 6.8% and 82.6% ± 7.9%, respectively (Fig. 1). No patients with secondary malignancy and severe cardiotoxicity were observed. Median follow-up period for all patients was 75 (range, 0–131) months.

Treatment-Related Mortality

Three deaths occurred that were not related to leukemia during induction therapy. Two of them occurred during the initial induction therapy, and the other occurred during second induction therapy.

TABLE II. Patients' Characteristic in the JCCLSG AML 9805 Down Study (N = 24)

Characteristic	No	%
Age, months		
Median	17	—
0–12	4	17
12–24	12	46
24–36	4	17
36–48	4	17
Sex		
Male	19	79
Female	5	21
History of TMD		
Yes	7	29
No	13	54
Unknown	4	17
Hepatomegaly		
Yes	10	42
No	12	50
Unknown	2	8
Splenomegaly		
Yes	10	42
No	12	50
Unknown	2	8
WBC, $\times 10^9$/L		
Median	6.5	—
Range	2.8–70.9	—
Hb, g/dL		
Median	8.1	—
Range	3.2–11.8	—
Plt, $\times 10^9$/L		
Median	26	—
Range	3–139	—
Cytogenetics		
Trisomy 8	5	21
Monosomy 7	4	17
Additional 21	2	8

Toxic Events

The incidence of grade 3 or 4 toxicity during induction and each intensification phase of therapy is shown in Table III. Three patients died during remission-induction therapy. One death was attributable to intracranial hemorrhage with disseminated intravascular coagulation, and the others were due to sepsis. The rate of induction death was 12.5%. No toxic deaths were observed during remission.

Prognostic Factors

Extramedullary invasion at initial diagnosis was a significant prognostic factor for 5-year EFS on univariate analysis ($P = 0.046$). Other factors, including sex, initial age, initial WBC, history of TMD, and chromosomal abnormality, were not significant.

DISCUSSION

The results of the JCCSLG AML 9805 Down study, which was conducted to evaluate the efficacy and safety of continuous and high-dose cytarabine combined chemotherapy with reduced intensity for AML-DS patients were presented. All patients enrolled in our study were younger than 4 years and had a phenotype of acute megakaryocytic leukemia (AMKL), which was consistent with previous reports for AML-DS. The number of patients was limited, but this regimen appears to be highly effective because there were no non-responders, and only one patient relapsed.

Contemporary clinical trials for AML-DS children are summarized in Table IV [5–11]. Treatment strategies for AML-DS are based on reduced intensity for AML non-DS, such as BFM and our study, or on a specifically designed strategy, such as the AT/DS study and the AML99 Down study in Japan [8,9]. The EFS of these studies, including the present study, has been between 80% and 90%.

The key drugs for the treatment of AML-DS are anthracyclines, cytarabine, and etoposide; it was also confirmed by in vitro studies that AMKL-DS blasts were significantly more sensitive to these drugs than non-DS AML cells [12]. AMKL-DS blasts are especially sensitive to cytarabine, possibly to the effect of the GATA1 mutations and trisomy 21 on the levels of cytarabine-metabolizing enzymes [13].

In the BFM 98 DS study, with a 3-year EFS of 89%, high-dose cytarabine (3 g/m^2) was used as intensification [6]. The authors reported that a high cure rate could be achieved in DS patients with therapy protocols including high-dose cytarabine. However, they also mentioned that it should be confirmed whether a dosage of 3 g/m^2 of cytarabine is necessary because of its toxicity. In

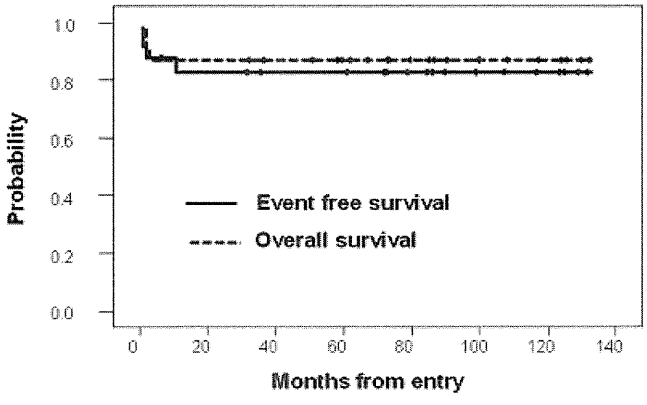

Fig. 1. Actuarial survival rate for the JCCLSG AML 9805 Down study. Of the 24 patients, 22 achieved CR. One patient relapsed. Two patients died during induction therapy. One patient died as a result of sepsis during the first CR. The 5-year overall survival (OS) was 87.5%, and the 5-year EFS was 82.6%.

TABLE III. Severe Adverse Events in the JCCLSG AML9805 Down Study (Grade III–IV)

Adverse events	AVC1-1 no.	n = 24 (%)	AVC1-2 no.	n = 22 (%)	MC no.	n = 21 (%)	EC no.	n = 21 (%)	AVC2 no.	n = 21 (%)
ALT/AST	5	23	2	9	0	0	1	5	0	0
Gastrointestinal	9	41	5	23	5	24	2	10	2	10
Renal	0	0	0	0	0	0	0	0	0	0
Cardiac	0	0	0	0	0	0	0	0	0	0
Pulmonary	1	5	0	0	0	0	0	0	0	0
Neurology	0	0	0	0	0	0	0	0	0	0
Pain	1	5	1	5	0	0	0	0	1	5
Fever/infection	14 (2)	64	9 (1)	41	11	52	15	71	7	33
Others	0	0	0	0	0	0	0	0	0	0

Number of patients who died.

our JCCLSG AML9805 Down study, 1 g/m^2 of cytarabine with etoposide was used for intensification. Serious non-hematological adverse effects, including infection, were not more frequent in this phase than in the other phase of this study (Table III). The dosage of 1 g/m^2 used in the present study may be sufficient for the treatment of AML-DS.

In the Japanese trial AML 99 Down study, the 4-year EFS was 83%, and treatment-related mortality was only 1.4%, which is much lower than that of recent reports for AML-DS [9]. However, relapse and induction failure were more frequent than in other reports with an intensive regimen. The regimen consisted of simple repeating of intermediate doses of pirarubicin and etoposide, so it is possible to reduce the rate of relapse and resistant disease using continuous and high-dose cytarabine combined chemotherapy, as in the JCCLSG AML9805 Down study.

As for other types of leukemia, risk-oriented therapy is proposed if any prognostic factors are identified in AML-DS. In the CCG 2891 study, patients with AML-DS who were older than 2 years had an increased risk of relapse [5]. However, in the BFM 98 DS study and in the Japanese AML 99 Down study, there was no difference in outcome between those 2 years or younger and those older than 2 years [6,9]. The present study also did not identify age older than 2 years as a risk factor, because all 7 patients older than 2 years survived without relapse after completing this protocol.

For cytogenetic factors, monosomy 7 is known to be a risk factor in children with AML [14,15]. In AML-DS, the presence of monosomy 7 adversely affected the outcome in the previous two Japanese trials, but not in the CCG 2891 study [5,8,9]. In the present study, four patients were found to have monosomy 7, and they all maintained remission. Continuous and high-dose cytarabine combined chemotherapy might affect intensification, which negates risk factors such as age and monosomy 7.

It is important to note that only one patient relapsed in the present study. Moreover, the cumulative doses of anthracycline and etoposide in this JCCLSG AML9805 Down study were lower than in other recent reports with intensive regimens for AML-DS. No patients had developed secondary cancer or cardiac insufficiency at the time of this analysis. The survival of DS patients has become longer, and it would be more important to decrease the late toxicity by reducing the cumulative doses of antileukemic drugs for AML-DS patients.

On the contrary, treatment-related mortality occurred in 3 of 24 patients (12.5%), which is more frequent than in other recent reports with intensive regimens for AML-DS. All three patients died from infection during the initial and second courses of this protocol. We could not identify any risk factors for toxicity in these patients, such as age or cardiac disease, compared with the patients who were successfully treated by this protocol. Serious non-hematological adverse effects, including infection, were more frequent during the remission induction phase than during the intensification phase. Induction therapy with combined continuous cytarabine might be toxic for AML-DS patients, although the induction rate is high. On the other hand, toxicity during the intensification phase including high-dose cytarabine was tolerable.

On the basis of the results of the previous Japanese trials and the present study, we have designed a risk-oriented therapy protocol for our next trial with AML-DS. Patients with M2, M3 marrow after induction therapy by pirarubicin, intermediate-dose cytarabine, and etoposide classified into a high-risk group will receive the continuous and high-dose cytarabine combined regimen of this JCCSLG AML9805 Down study.

TABLE IV. Comparison of Recent Clinical Trials for AML-DS

Study	Registry (year)	N	Daunorubicin (mg/m^2)	Ara-C (mg/m^2)	Etoposide (mg/m^2)	TRM (%)	OS (%)	EFS (%)
BFM98 for DS	1998–2003	67	220–240	23–29,000	950	5	91	89 (3y)
BFM93	NA	51	220–400	23,000	950	4	70	68 (3y)
NOPHO AML93	1988–2002	41	300	48,600	1,600	5	NA	85 (8y)
MRC AML10/12	1988–2002	46	670	10,600	NA	15	74	74 (5y)
CCG 2861/2891	1989–1999	160	320	15,800	1,600	4	79	77 (6y)
POG 9421	1995–1999	57	100	20,700	—	0	NA	79 (3y)
AT/Down	1987–1997	33	100–400	4,200	2,700	9	NA	80 (8y)
AML99 DS	2000–2004	72	250	3,500	2,250	1	84	83 (4y)
JCCLSG 9805DS	1998–2006	24	190	12,600	200	12.5	88	83 (5y)

TRM, treatment-related mortality; OS, overall survival; EFS, event-free survival; NA, not evaluated.

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■ 特集 心のケア

悪性腫瘍の患児と両親への精神的サポート —医師の立場から

工 藤 寿 子*

はじめに

小児の悪性腫瘍性疾患の予後は過去30年間で飛躍的に改善しており，現在では7割以上に治癒が期待できる時代になっている。長期生存者が増えるにしたがい，小児がんを心的外傷としてとらえ，患者・家族の抱える心理的苦痛を評価し，支援する精神的サポートに目を向ける余裕が生じてきた[1~4]。本稿では，当科の取り組みを述べるとともに，フィラデルフィア小児病院がんセンターにおける心的外傷後ストレス障害（PTSD）を予防する取り組みについて紹介したい。

Ⅰ．静岡県立こども病院血液腫瘍科の取り組み

われわれは1990年ごろより静岡県内のほかの小児がん治療施設とともに，悪性腫瘍の患者と家族に対するトータルケアを進めてきた。以下，当科における精神的サポートの概略を，時期別に分けて述べる。

1．入院時の精神的サポート

当科では悪性腫瘍患者には入院時より担当看護師を決めて，主治医とともに患者・家族への説明に同席するようにしている。入院当初は病名告知，検査や手術予定，治療スケジュール，予想される予後や晩期合併症など立て続けに説明を受け，多くの両親は頭が真っ白になって，何を聞いたか覚えていないとあとから振り返っていわれることがある。説明内容は複写形式にしてご家族に手渡すことをしている。別途，入院セットを用意して，家族が必要とする情報を提供できるよう配慮しており，ソーシャルワーカーが面談をし，申請書類などの相談にのっている。

2．入院中の精神的サポート

子どもたちは突然入院を余儀なくされ，学校生活や修学旅行の予定など，当たり前のように過ごしてきた日常生活から病院での生活が始まる。子どもたちの知的な発達水準を考慮して，繰り返し病気や治療についての対話を行い，不安を取り除き治療への協力が得られるよう配慮が必要である。病棟保育士が学童・乳児病棟それぞれに配属され，訪問学級に通学できない子どもたちや乳幼児に遊びや歌，本の読み聞かせなどを通して，子どもたちの療養環境の改善に努めている。

また，セラピードッグのベイリーと看護師の資格を持ったハンドラーが治療に携わっている。ベイリーが当院に来てから，以前は手術や検査を嫌がっていた子どもたちがベイリーと一緒だと笑顔で受けられるようになり，子どもたちの治療への前向きな姿勢を促す取り組みも期待されている。

造血細胞移植を受ける患者については，毎回，移植カンファレンスを行っている。カンファレンスには医師，看護師，薬剤師，検査技師，栄養士，作業療法士，訪問学級教師，病棟保育士など多職種が集まり，個々の症例について意見を出し合い，移植医療という厳しい治療に向けてそれぞれの役割を確認しあう。チャイルドライフスペシャリスト（CLS）から，絵本や人形などを使って，放射線照射や無菌室の説明が行われる。

当院では2009年に緩和ケアチームが発足した。構成メンバーは医師6名（麻酔科1名，緩和ケア医1名，血液腫瘍科2名，児童精神科医2

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