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Prognostic impact of karyotypic findings in childhood acute lymphoblastic leukaemia: a Nordic series comparing two treatment periods

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Summary. The prognostic impact of acquired chromosome abnormalities was evaluated in a population-based consecutive series of 768 children (< 15 years of age) with acute lymphoblastic leukaemia (ALL). The study cohort included all cases of cytogenetically abnormal childhood ALL diagnosed between 1986 and 1997 in the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). The probability of event-free survival (pEFS) for the total cohort was 0·72 ± 0·02. When comparing the two treatment periods of July 1986 to December 1991 and January 1992 to December 1997, a better survival was seen for the latter time period (pEFS of 0·69 ± 0·02 vs. 0·76 ± 0·02, $P = 0·05$). Hypodiploidy with less than 45 chromosomes, t(9;22)(q34;q11) and 11q23 translocations were associated with a dismal outcome during the whole study period (pEFS of 0·57 ± 0·12, 0·41 ± 0·14 and 0·37 ± 0·10 respectively). The poor prognostic influence of 11q23 rearrangements seemed to be restricted to infants and older children (> 10 years), who differed significantly from children aged 1–10 years in this regard ($P < 0·01$). Patients with t(9;22)-positive ALL seemed to benefit from allogeneic bone marrow transplantation in first remission ($P = 0·05$). The pEFS for children with t(1;19)(q23;p13)-positive ALL was intermediate (0·63 ± 0·17), with a tendency to a better outcome for patients with the unbalanced variant der(19)t(1;19). Hyperdiploid ALL patients, subdivided into moderate hyperdiploidy (47–51 chromosomes), massive hyperdiploidy (52–60 chromosomes) and cases in the tri-/tetraploid range (> 60 chromosomes) had the best outcome in the last treatment period (pEFS of 0·81 ± 0·06, 0·80 ± 0·04 and 0·88 ± 0·07 respectively), unless t(1;19), t(8;14), t(9;22) or 11q23 translocations were present. In a multivariate analysis including white blood cell (WBC) count, immunophenotype, age, mediastinal mass, central nervous system involvement and leukaemia karyotype, only WBC and modal chromosome number were shown to be significant independent risk factors ($P < 0·01$).

Keywords: acute lymphoblastic leukaemia, children, karyotype, prognosis.

Different cytogenetic abnormalities have repeatedly been shown to provide prognostically important information in childhood acute lymphoblastic leukaemia (ALL). For example, hyperdiploidy is associated with a favourable outcome, whereas 11q23 translocations, t(9;22)(q34;q11) and hypodiploidy confer a dismal prognosis. Taking the leukaemia karyotype into account when stratifying ALL patients into different treatment modalities has therefore contributed significantly to the better survival seen during recent years (Lampert *et al*, 1991; Harbott *et al*, 1993; Pui, 1995; Behm *et al*, 1996; Chessells *et al*, 1997; Forestier *et al*, 1997; Uckun *et al*, 1998a).

Many previous studies of the clinical usefulness of cytogenetics in ALL were not population based. The possible selection bias this entails, together with the often heterogeneous treatment given, preclude firm conclusions as

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Table I. Clinical and risk group data on the 1925 children with ALL, stratified according to cytogenetic features.

	Study cohort							
Clinical features and risk group data	< 44 chr $n = 20$	45–46 chr $n = 264$	47–51 chr $n = 136$	52–60 chr $n = 304$	> 60 chr $n = 44$	Total $n = 768$	Normal karyotype $n = 571$	No cytogenetic results $n = 626$
WBC $\times 10^9$/l median (range)	20 (3–737)	21 (1–973)	14 (1–685)	7 (1–320)	11 (1–66)	10 (1–973)	10 (1–1400)	12 (1–998)
Age in months median (range)	72 (2–167)	63 (1–180)	57 (13–119)	44 (8–180)	60 (0–177)	50 (0–180)	56 (0–180)	50 (2–180)
Standard risk (%)*	14	17	29	42	27	30	32	31
Intermediate risk (%)*	42	26	33	40	41	34	34	34
High/very high risk (%)*	28	42	35	16	29	29	28	27
Special group (%)*	14	13	< 1	< 1	2	5	3	5
T-cell ALL (%)	10	11	3	< 1	2	5	14	11
Mediastinal mass (%)	10	8	4	2	4	5	7	3
CNS involvement (%)	0	2	1·5	2	2	2	2	2
Risk karyotype†	14	19	8	< 1	0	7	–	–

*Risk group classification according to Gustafsson *et al* (1998).
†Includes t(1;19), t(8;14), t(9;22)/del(22q) and 11q23 translocations.
ALL, acute lymphoblastic leukaemia; chr, chromosomes; WBC, white blood cells; CNS, central nervous system.

regards the true prognostic impact of ALL-associated chromosomal changes. The five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden; total population 22 million) have, during the last two decades, had a common registry for all childhood ALL (< 15 years of age) and, since 1986, the same risk classification and treatment protocols. The aim of the present study was to evaluate associations between karyotypic patterns, with emphasis on characteristic chromosomal rearrangements and modal numbers, and survival during two time periods with different treatment protocols in this Nordic population-based consecutive cohort of childhood ALL patients.

PATIENTS AND METHODS

Patients. A total of 1965 children below the age of 15 years were diagnosed with ALL in the five Nordic countries from 1 July 1986 to 31 December 1997. In 1197 cases, either a normal ($n = 571$) or no karyotype ($n = 626$) was registered. Thus, clonal abnormalities were found in the leukaemic cells in 768 cases. No patient was lost to follow-up.

Two different treatment protocols – NOPHO (Nordic Society of Paediatric Haematology and Oncology) ALL-86 and NOPHO ALL-92 – were used during the study period. Protocols were changed on 1 January 1992. These two time periods (1986–91 and 1992–97) included 290 and 478 cases with clonal chromosomal abnormalities respectively. Risk classification during both treatment periods was based on age, white blood cell (WBC) count and immunophenotypic and karyotypic features, dividing the ALL into standard risk [SR; age 2–10 years, WBC $< 10 \times 10^9$/l and no high risk (HR) features], intermediate risk (IR; 1–2 years or > 10 years, WBC = 10–50 $\times 10^9$/l and no HR features), high risk [HR; WBC $> 50 \times 10^9$/l, central nervous system (CNS) or testicular leukaemia, t(9;22),t(4;11), T-cell immunophenotype], very high risk (VHR; lymphomatous leukaemia, together with other HR criteria) and special group (SG; < 1 year of age or B-cell leukaemia). The treatment protocols and the risk stratification have been reported previously (Gustafsson *et al*, 1998). The intensification carried out from NOPHO ALL-86 to NOPHO ALL-92 may be summarized as an introduction of pulses of high-dose methotrexate infusions and of early and/or delayed intensification courses.

Cytogenetics. Bone marrow and/or peripheral blood samples were cytogenetically analysed using standard methods by different laboratories in the Nordic countries. During the last few years, fluorescence *in situ* hybridization (FISH) analyses have been increasingly used to verify, or to describe more precisely, the changes found. The clonality criteria and the description of abnormalities have followed the recommendations of the International System for Human Cytogenetic Nomenclature, the most recent being ISCN (1995). All patients were registered on the NOPHO data base. The cases were divided into five different modal groups based on the main modal number distribution: group 1, < 45 chromosome (hypodiploidy); group 2, 45–46 chromosomes (moderate hypodiploidy and pseudodiploidy);

group 3, 47–51 chromosomes (moderate hyperdiploidy); group 4, 52–60 chromosomes (massive hyperdiploidy); and group 5, > 60 chromosomes (tri- and tetraploid range).

Statistics. Children alive in continuous complete remission (CCR) were censored on 31 December 1998. Patients in CCR in the first treatment period were followed for 84–150 months and in the second from 12 to 84 months. The time to an adverse event was defined as the interval between diagnosis and the respective event (relapse, death in CCR or second malignancy). Children who did not achieve remission were assigned a time of zero. Statistical analyses were performed using the SPSS statistical software for Macintosh. Prognostic factors were identified using Cox's multiple proportional hazard model, including the following variables: WBC, age at diagnosis, immunophenotype, presence of mediastinal mass (MM) and CNS involvement. Life tables were constructed using the Kaplan–Meier method and the prognostic differences among subgroups were tested with the log rank method (Cox, 1972; Nourusis, 1994). The limit for significance in all analyses was $P = 0{\cdot}05$. When comparing the outcome among the various modal groups, cases with structural rearrangements known to confer poor prognosis, i.e. t(1;11)(p32–36;q23), t(1;19)(q23;p13), t(4;11)(q21;q23), t(8;14) (q24;q32), t(9;11)(p21;q23), t(9;22)(q34;q11) and t(11;19) (q23;p13) were excluded.

RESULTS

Basic clinical data

ALL patients not included in the study, i.e. cases with a normal karyotype or without cytogenetic results ($n = 1197$), and the study cohort ($n = 768$) displayed the same risk group distributions, and the two patient groups did not differ with regard to WBC counts, age, MM or CNS involvement. T-cell ALL, on the other hand, was less frequent in the study cohort (Table I).

Probability of event-free survival (pEFS) in the different modal groups

The outcome was best for the hyperdiploid groups with pEFS of 0·73–0·79 (the pEFS was 0·80–0·88 in the second treatment period), intermediate for the 45–46 chromosome group with pEFS of 0·71 (pEFS 0·71 in the second period) and poor for the hypodiploid group (pEFS 0·57) (Table II). The differences among the modal subgroups were significant in a univariate analysis ($P < 0{\cdot}01$). In the multivariate analysis, only WBC and modal number were shown to be significant independent risk factors ($P < 0{\cdot}01$). Clinical risk factors, i.e. high WBC and MM, were more frequent among patients with hypodiploid and pseudodiploid ALL than among those with hyperdiploid ALL, and the t(1;19), t(8;14), t(9;22) and 11q23 translocations were rarely seen in the hyperdiploid ALL (Table I). Thus, ALL patients with modal number < 47 were more often classified as non-SR and, hence, more intensively treated than those with > 46 chromosomes. Modal number distributions for all patients are shown in Fig 1. A total of 14 hyperdiploid ALL carried t(1;19), t(8;14), t(9;22) or 11q23 translocations and the pEFS (0·38 ± 0·17) for these children was significantly lower than the pEFS for patients with hyperdiploid ALL not harbouring these risk translocations ($P < 0{\cdot}01$; Fig 2).

Table II. Probabilities of event-free survival (pEFS) in the various cytogenetic subgroups.

Cytogenetic subgroup	Number cases of	pEFS			
		1986–97	1986–91	1992–97	*P*-value
t(4;11)(q21;q23)	16	0·29 ± 0·13			
t(11;19)(q23;p13)	10	0·33 ± 0·8			
All 11q23 translocations	29	0·37 ± 0·10			
t(9;22)(q34;q11)/del(22q)	17	0·41 ± 0·14			
t(1;19)(q23;p13)/der(19)t(1;19)	10	0·63 ± 0·17			
t(8;14)(q24;q32)	8	0·75 ± 0·15			
< 45 chromosomes*	17	0·57 ± 0·12			
45–46 chromosomes*	213	0·71 ± 0·04	0·72 ± 0·05	0·71 ± 0·01	ns
47–51 chromosomes*	125	0·75 ± 0·04	0·66 ± 0·07	0·81 ± 0·06	ns
52–60 chromosomes*	302	0·79 ± 0·03	0·77 ± 0·04	0·80 ± 0·04	ns
> 60 chromosomes*	43	0·73 ± 0·09	0·64 ± 0·13	0·88 ± 0·07	ns
del(11q)	15	0·74 ± 0·13			
t/del(12p)	35	0·66 ± 0·11			
i(17)(q10)	8	0·80 ± 0·18			
Study cohort	768	0·72 ± 0·02	0·69 ± 0·02	0·76 ± 0·02	0·05
Normal karyotype	571	0·76 ± 0·02	0·71 ± 0·03	0·81 ± 0·02	0·02
No cytogenetic results	626	0·71 ± 0·02	0·68 ± 0·03	0·81 ± 0·03	0·03
All patients	1965	0·68 ± 0·02	0·63 ± 0·02	0·80 ± 0·01	< 0·01

*Excluding cases with t(1;19), t(8;14), t(9;22) and 11q23 translocations.
ns, not significant.

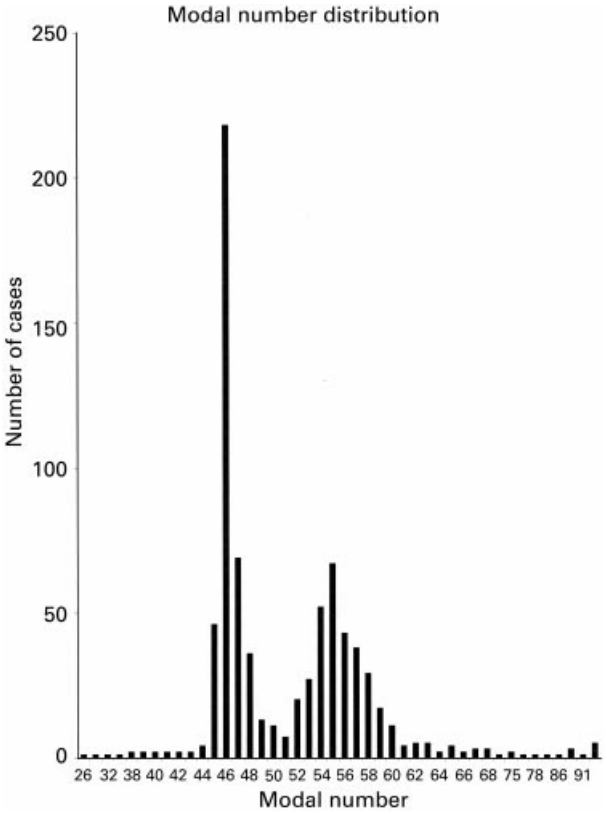

Fig 1. Modal number distribution among the 768 cytogenetically abnormal cases of childhood ALL.

Three of these 14 patients – all with t(9;22)-positive ALL – underwent allogeneic bone marrow transplantation (allo-BMT) in first remission and are still in CCR.

pEFS of ALL with characteristic structural chromosome rearrangements

Ten ALL cases had t(1;19), either as a balanced translocation ($n = 6$) or as the unbalanced der(19)t(1;19) ($n = 4$). Although all these ALL were classified as non-SR and all were intensively treated, the pEFS for this group was only 0·63 (Table II). All relapses ($n = 3$) were found in the subgroup with the balanced variant.

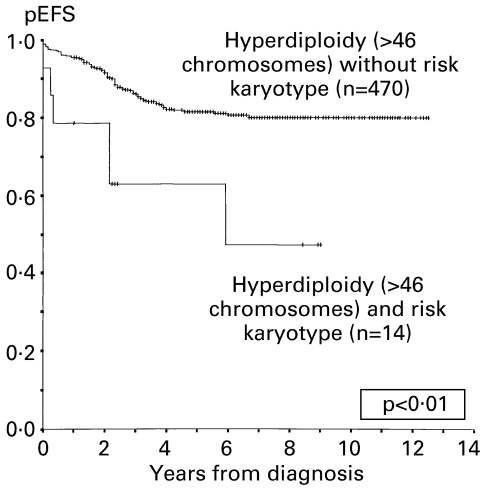

Fig 2. Prognostic impact of the t(1;19), t(8;14), t(9;22), and 11q23 translocations in hyperdiploid ALL.

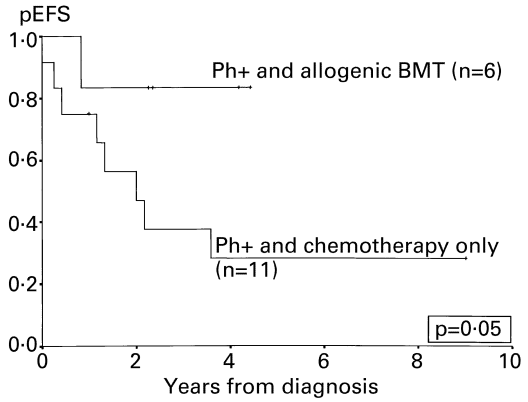

Fig 3. Survival differences between patients with Philadelphia (Ph) chromosome-positive ALL treated with or without allogeneic BMT in first remission.

A total of 17 ALL with the Philadelphia (Ph) chromosome were identified – 13 had the reciprocal (9;22)(q34;q11) and four had del(22q) only – and the pEFS of this group was 0·41 (Table II). A significantly ($P = 0·05$) better outcome for Ph-positive ALL treated with allo-BMT was noted (Fig 3).

The ALL cases with 11q23 translocations – including t(1;11)(p32–p36;q23), t(4;11)(q21;q23), t(9;11)(p21;q23) and t(11;19)(q23;p13) – had as a group an inferior prognosis (pEFS = 0·37; Table II), although a better outcome was seen for patients aged 1–10 years than for infants and older children ($P < 0·01$) (Fig 4). The karyotypic and clinical features of the seven children in the intermediate age group still in CCR are listed in Table III. Only one patient, an infant, with 11q23-positive ALL underwent allo-BMT in first remission. The pEFS for the cases with deletions involving 11q, 30% of them with

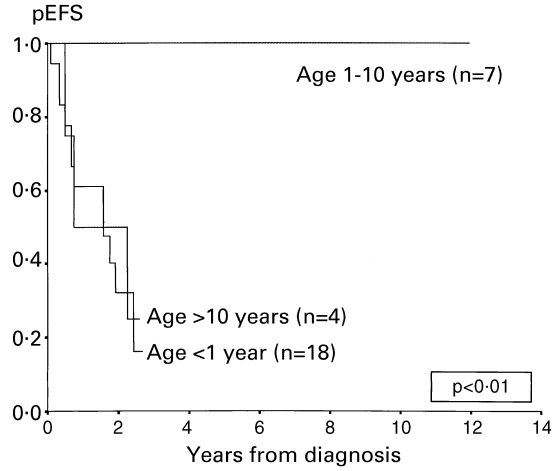

Fig 4. Event-free survival (EFS) in 29 cases of childhood ALL with 11q23 translocations, according to age.

Table III. Karyotypic and clinical features of the seven children aged 1–10 years with 11q23-positive ALL who are still in CCR.

Karyotype	Sex	Age	WBC $\times 10^9$/l	CNS	MM	Time in CCR (months)
46XX,t(4;11)(q21;q23)	F	1 year 7 months	152	No	No	143
46,XY,t(4;11)(q21;q23)	M	5 years 9 months	570	No	No	131
47XX,+X,t(4;11)(q21;q23)/47,XX,+mar	F	7 years	15	No	No	107
46XX,t(9;11)(p21;q23)	F	9 years 8 months	5	No	No	77
46XX,t(11;19)(q23;p13)	F	2 years 7 months	275	No	Yes	122
46,XY,t(11;19)(q23;p13)	M	8 years 10 months	224	No	No	45
46,XY,t(11;19)(q23;p13)	M	1 year 3 months	2	No	No	19

CCR, continuous complete remission (censor date 31 December 1998); WBC, white blood cells; CNS, central nervous system; MM, mediastinal mass.

breakpoints at 11q23, did not differ from that of the total study cohort (Table II).

The frequencies of other characteristic ALL-associated abnormalities were generally too low to allow meaningful statistical analyses. The pEFS of the more common changes, i.e. t(8;14), t/del(12p) and i(17q), were quite similar to the pEFS of the entire study group (Table II).

Comparison between treatment periods

A better outcome was seen for the total study cohort in the second treatment period, with pEFS increasing from 0·69 to 0·76 ($P = 0·05$; Table II). No significant improvements were found for any of the cytogenetic subgroups, although a tendency for a better survival of patients with hyperdiploid ALL was noted (Table II). However, shifts in risk group stratifications occurred between the two treatment periods; in the moderately hyperdiploid subgroup, the proportion of patients treated as SR decreased from 35% to 25%, whereas the proportion treated as IR and HR/VHR increased from 29% to 35% and 33% to 37% respectively.

DISCUSSION

In the present study, no significant clinical differences were noted between the study cohort and cases with normal karyotypes or without cytogenetic information, except that T-cell ALL was less frequent in the study cohort (Table I). This strongly indicates that the group of patients with cytogenetically abnormal ALL was unselected, i.e. there has been no clinical bias in sending cases for cytogenetic investigations and no particular clinical subsets of childhood ALL are more likely to fail attempted cytogenetic investigation. Thus, we consider the study cohort to be representative of the entire population of children with ALL diagnosed and treated in the Nordic countries between 1986 and 1997.

The salient findings of this population-based series of cytogenetically investigated childhood ALL were the significant differences in survival observed among the various karyotypic modal groups, that the ALL-associated rearrangements t(1;19), t(9;22) and 11q23 translocations were associated with a dismal outcome (also when occurring in the context of hyperdiploidy) and that the prognostic impact of 11q23 translocations is modified by age.

Because of the strong association between some ALL-related chromosomal rearrangements, i.e. t(1;19), t(8;14), t(9;22) and 11q23 translocations, and outcome (Lampert *et al*, 1991; Harbott *et al*, 1993; Pui, 1995; Behm *et al*, 1996; Chessells *et al*, 1997; Forestier *et al*, 1997; Uckun *et al*, 1998a), cases with these changes were excluded in the initial survival analyses of the different modal number groups (Table II). A multivariate analysis of all the remaining cases, the vast majority, disclosed that only WBC and modal number were independent risk factors, i.e. age, MM and CNS involvement lost their prognostic significance. The finding that age seemed to be less important may well be explained by the fact that it is strongly associated with some of the specific translocations excluded from the multivariate analysis, i.e. most 11q23 translocations are found in young children, particularly infants, and the incidence of Ph-positive ALL increases with age (Pui, 1995). It is noteworthy in this context that the pEFS for patients with hyperdiploid ALL decreased significantly if t(1;19), t(8;14), t(9;22) or 11q23 translocations were present (Fig 2). It is well known that, although a group of patients in the low-risk category probably would also have been cured with less intensive therapy, many patients fail on traditional chemotherapy despite favourable clinical and cytogenetic prognostic features. The finding that the presence of the abovementioned rearrangements in hyperdiploid karyotypes was a negative prognostic factor could indicate that they or their equivalents remained undetected in some of the cases with poor outcome in the hyperdiploid group. This could be due to the usually poor technical quality of metaphase spreads seen in hyperdiploid ALL, or submicroscopic abnormalities leading to the same fusion genes may have been present.

Among the ALL-associated chromosomal rearrangements assessed in this study, only t(1;19), t(9;22) and 11q23 translocations were sufficiently numerous to allow meaningful survival analyses. Other recurrent abnormalities identified, such as del(6q), i(17q) and del(17p), were mostly detected in complex karyotypes, supporting the notion that these unbalanced aberrations are secondary changes

without any obvious impact on survival (Johansson *et al*, 1994). It has previously been suggested that i(17q) could be a negative prognostic factor in ALL, especially in cases with hyperdiploid karyotypes (Pui *et al*, 1988), but such an association could not be seen in our series. On the contrary, the pEFS for ALL with i(17q) was 0·80 (Table II), suggesting that this isochromosome could be an indicator of good prognosis. However, the i(17q) was found in only eight ALL and more cases with this change, preferably treated in a similar manner, are needed before any firm conclusions can be drawn as regards its prognostic impact.

A total of 35 ALL with abnormalities of the short arm of chromosome 12 were identified. It has previously been reported that the *ETV6* gene is rearranged, often fused to *CBFA2* as a result of the cryptic t(12;21)(p13;q22), in most ALL with t/del(12p) and that the t(12;21) is associated with a favourable prognosis, admittedly with conflicting claims made regarding the risk of relapse (Harbott *et al*, 1997; Raimondi *et al*, 1997; Loh *et al*, 1998; Rubnitz *et al*, 1999). Owing to the time span of the present study, i.e. most cases were investigated before the t(12;21) had been identified, only a few ALL were investigated for the presence of this translocation. However, the fact that t/del(12p) aberrations were never identified in the massive hyperdiploidy group in our study and that t(12;21) rarely, if ever, occurs in ALL with >51 chromosomes (Rubnitz *et al*, 1999) could indirectly suggest that many of the present cases with 12p abnormalities had a cryptic t(12;21). If so, the pEFS (0·66; Table II) for that patient group does not support a particularly favourable outcome.

The relatively low pEFS for the 10 patients with t(1;19)-positive ALL (Table II) supports previous assertions that this abnormality may be associated with treatment failure, even in patients receiving intensive therapy (Christi *et al*, 1990; Secker-Walker *et al*, 1992; Chessells *et al*, 1997; Uckun *et al*, 1998b). The prognostic impacts of the balanced and unbalanced variants of this translocation seem to differ (Secker-Walker *et al*, 1992; Uckun *et al*, 1998b) and it is possible that only the reciprocal t(1;19) makes the patient eligible for intensified treatment, possibly including allo-BMT. It is noteworthy that all relapses in the present study occurred in the group with the balanced variant, although this difference did not reach statistical significance. The 1;19 translocation, or rather the resulting fusion gene *E2A–PBX1*, can be detected by reverse transcriptase polymerase chain reaction analysis, which has been shown to increase the detection rate for this rearrangement (Hunger, 1996). However, if the differences in survival between patients with the balanced and unbalanced variants of the 1;19 translocation are borne out and if future treatment protocols are going to differ for these two patient categories, then chromosome banding or FISH investigations will be mandatory because only these methods can distinguish between the cytogenetic variants.

As in many previous studies, patients with Ph-positive ALL in our series had a dismal prognosis with a pEFS of only 0·41 (Table II). Although based on only few patients, our data indicate that allo-BMT in first remission, regardless of other clinical and cytogenetic risk parameters, significantly increases the likelihood of long-term survival (Fig 3). The strong association between the presence of a Ph chromosome and poor outcome, the possibility of cure when allo-BMT is used and the occasional finding of t(9;22) in hyperdiploid karyotypes, which often have a poor chromosome morphology, argues for the use of additional, i.e. molecular genetic, methods to search for this translocation in all childhood ALL.

The 11q23 translocations that were identified, all known to involve the *MLL* gene (Mitelman *et al*, 1997), conferred a poor prognosis, irrespective of ploidy level (Table II; Fig 2) but not of age, inasmuch as only children less than 1 year and more than 10 years of age seemed to be affected (Fig 4). A better survival for children aged 1–10 years with t(4;11)-positive ALL has previously been reported (Pui *et al*, 1994; Johansson *et al*, 1998). Among all the 11q23 translocations of our series, approximately one-third were t(11;19) (Table II), and our data thus suggest that the favourable prognosis in this intermediate age group not only applies to t(4;11) but also to t(11;19). It is evident that age should be included as one important parameter when stratifying 11q23-positive ALL into different therapy protocols. Finally, the poor overall survival for childhood ALL with 11q23 rearrangements, excluding deletions which rarely involve the *MLL* gene and which are not associated with a dismal prognosis (Table II; Raimondi *et al*, 1995; Harbott *et al*, 1998), as well as with some of the other chromosomal aberrations mentioned above emphasizes the continuous need to search for novel treatment strategies in this disease.

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