Clinical and Cytogenetic Features of a Population-Based Consecutive Series of 285 Pediatric T-Cell Acute Lymphoblastic Leukemias: Rare T-cell Receptor Gene Rearrangements Are Associated with Poor Outcome

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Clinical characteristics and cytogenetic aberrations were ascertained and reviewed in a population-based consecutive series of 285 pediatric T-cell acute lymphoblastic leukemias (T-ALLs) diagnosed between 1992 and 2006 in the Nordic countries. Informative karyotypic results were obtained in 249 (87%) cases, of which 119 (48%) were cytogenetically abnormal. Most (62%) of the aberrant T-ALLs were pseudodiploid. Structural changes were more common than numerical ones; 86% displayed at least one structural abnormality and 41% at least one numerical anomaly. The most frequent abnormalities were T-cell receptor (TCR) gene rearrangements (20%) [TCR;11p13 (10%), TCR;10q24 (3%), TCR;other (8%)], del(9p) (17%), +8 (14%), del(6q) (12%), and 11q23 rearrangements (6%). The TCR;other group comprised the rare rearrangements t(X;14)(p11;q11), t(X;7)(q22;q34), t(1;14)(p32;q11), ins(14;5)(q11;q?q?), inv(7)(p15q34), t(8;14)(q24;q11), t(7;11)(q34;p15), and t(12;14)(p13;q11). The clinical characteristics of this Nordic patient cohort agreed well with previous larger series, with a median age of 9.0 years, male predominance (male/female ratio 3.1), median white blood cell (WBC) count of 66.5 $\times$ 10^9/l, and a high incidence of mediastinal mass and central nervous system involvement (59% and 9.5%, respectively). These features did not differ significantly among the various genetic subgroups. 5-year event-free survival (EFS) and overall survival for all patients were 0.61 ($\pm$0.03) and 0.67 ($\pm$0.03), respectively. In a multivariate analysis, two factors affected negatively the EFS, namely a WBC count of $\geq$200 $\times$ 10^9/l ($P < 0.001$) and the presence of rare TCR rearrangements ($P = 0.001$). In conclusion, in this large series of childhood T-ALLs from the Nordic countries, the cytogenetic findings were not associated with risk of therapy failure with the exception of the TCR;other group. However, further prospective and collaborative investigations of this genetically heterogeneous entity are needed to confirm these results.

INTRODUCTION

T-cell acute lymphoblastic leukemia (T-ALL) represents ~15 and 25% of pediatric and adult ALL, respectively (Graux et al., 2006). Compared with B-cell precursor ALLs, T-ALLs are more often cytogenetically normal, and they hence

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represent a minority of all reported ALL cases with an aberrant karyotype. In fact, less than 650 cytogenetically abnormal T-ALLs in children and adolescents have been published (Mitelman et al., 2009). This notwithstanding, several characteristic chromosomal abnormalities have been identified in this disease entity, with the most typical being rearrangements involving the T-cell receptor (TCR) loci, mainly the *TRA@/TRD@* genes at 14q11 and the *TRB@* gene at 7q34. These loci are prone to recombine illegitimately with several different oncogenes that, as a consequence, become aberrantly expressed, such as genes encoding transcription factors (e.g., various homeobox genes) and genes coding for proteins involved in protein-protein interaction (i.e., *LMO1* at 11p15 and *LMO2* at 11p13) (Aifantis et al., 2008). Other common chromosomal changes in T-ALL include loss of 6q and 9p material and gain of chromosome 8 (Schneider et al., 2000). Apart from these cytogenetically visible changes, an increasing number of cryptic genetic changes has been discovered by the use of fluorescence in situ hybridization (FISH) and molecular genetic analyses, for example the *PICALM/MLLT10* [t(10;11)(p12;q14)] and *NUP214/ABL1* [t(9;9)(q34;q34), episomal or hsr] fusion genes, overexpression of *TLX3* (5q35) and *TAL1* (1p32), *MYB* (6q23) duplications, *CDKN2A* (9p21) deletions, and mutations of *NOTCH1* and *FBXW7* at 9q34 and 4q31, respectively. Taken together, the vast majority of T-ALLs are now known to harbor one or several genetic changes, in agreement with a multistep leukemogenic process (Van Vlierberghe et al., 2008).

Some of the above-mentioned aberrations have been associated with outcome, albeit at times with contradictory results (Van Vlierberghe et al., 2008). Although the clinical usefulness of the genetic features of T-ALLs is not at all on a par with the prognostic impact of several abnormalities in B-lineage ALLs, some T-ALL-associated aberrations have nevertheless emerged as possible risk-stratifying markers, with *TAL1* and *TLX1* overexpression being associated with a more favorable outcome and *PICALM/MLLT10* and *TLX3* overexpression correlating with a poor prognosis (Cavé et al., 2004; Bergeron et al., 2007; Ballerini et al., 2008; van Grotel et al., 2008). As regards *NOTCH1* and *FBXW7* mutations, they have been associated with a good prognosis in some but not all investigations (Breit et al., 2006; Zhu et al., 2006; Malyukova et al., 2007). Hence, additional studies are clearly needed to clarify the clinical impact of most genetic changes in T-ALL.

To investigate further the clinical and genetic features of pediatric T-ALL, we ascertained and reviewed all 285 children and adolescents diagnosed with T-ALL in the Nordic countries 1992–2006. In addition, the impact of different cytogenetic aberrations and clinical parameters on outcome was analyzed to identify factors of prognostic importance in a population-based patient cohort.

MATERIALS AND METHODS

Patients and Treatment Protocols

All cases ($n = 285$) of pediatric (<18 years) T-ALL diagnosed between 1992 and 2006 in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) were included in the study. The date of last follow-up was January 31, 2008, and the median follow-up time was 90 months (range, 12–192 months). The immunophenotypic diagnosis of T-ALL was performed according to EGIL (Bene et al., 1995). During the 1992–2006 time period, two different treatment protocols were used, namely NOPHO-ALL-1992 (158 patients) and NOPHO-ALL-2000 (123 patients). Four infants received treatment according to specific infant protocols and are not included in the survival analyses. NOPHO-ALL-1992 has been described in detail (Gustafsson et al., 2000), while the NOPHO-ALL-2000 is as yet unpublished. In brief, NOPHO-ALL-1992 stratified T-ALL patients into two risk groups—the high risk ($n = 56$) and the very high risk ($n = 102$) groups—with the latter comprising patients $\geq$5 years and white blood cell (WBC) counts $\geq 50 \times 10^9$/l, mediastinal mass, central nervous system (CNS)/testicular involvement, or slow response to initial induction therapy (M3 bone marrow at day 15 or >M1 bone marrow at day 29). NOPHO-ALL-2000 stratified the patients into three groups: intensive ($n = 28$), very intensive ($n = 50$) [>5 years, and WBC 100.1–200 $\times 10^9$/l, or CNS involvement or mediastinal mass] and extra intensive ($n = 45$) [WBC >200 $\times 10^9$/l, slow response, or 11q23 rearrangement]. Informed consent was obtained from the patients and/or their guardians in accordance with the Declaration of Helsinki.

Cytogenetic Studies

Chromosome banding analyses were performed on bone marrow samples (or peripheral blood in a

few instances) using standard methods in 15 cytogenetic laboratories in the Nordic countries. It should be emphasized that the number of metaphases analyzed and culture media have varied over the time span 1992–2006. However, in the vast majority of cases, more than 10 metaphases were investigated. All abnormal karyotypes have been centrally reviewed annually since 1996 (Sweden)/2000 (all five Nordic countries). FISH analyses have, during the last decade, been increasingly applied to either verify or characterize more precisely the chromosomal abnormalities found. Screening for cryptic changes, such as *CDKN2A* deletions, has not been performed on a regular basis.

Statistical Methods

The SPSS software 16.0 for Windows was used for all calculations. The probabilities of event-free survival (pEFS) and overall survival (pOS) were calculated using the Kaplan–Meier method, and the different cytogenetic and clinical subgroups were compared using the log rank test. The significance limit for P values was set to 0.05 in all tests, and all tests were two-sided. In the analysis of EFS, events consisted of induction failure, relapse, death in remission 1, and second malignant neoplasms. In the analysis of OS, death was the end point. The χ^2 test with exact calculation of P value was used to investigate possible correlations between cytogenetic groups and clinical characteristics. Multivariate analysis using a Cox regression model was performed to identify cytogenetic and clinical factors that had an independent impact on EFS. The following parameters were included in the analysis: gender, age, WBC count, mediastinal mass, CNS involvement, treatment protocol, and cytogenetic groups.

RESULTS

Patient Characteristics

The patient characteristics are summarized in Table 1. The total cohort had a male/female ratio of 3.1, a median age at diagnosis of 9.0 years, and a median WBC count of 66.5×10^9/l. Mediastinal and CNS involvement were seen in 59% (169 of 285) and 9.5% (27 of 285) of patients, respectively. The pEFS and pOS at 5 years were 0.61 ($\pm$0.03) and 0.67 ($\pm$0.03), respectively. The pEFS and pOS did not differ between the NOPHO-ALL-1992 and NOPHO-ALL-2000 protocol patients. The only clinical factor significantly affecting outcome was a WBC count $\geq 200 \times 10^9$/l (Table 2).

Based on the cytogenetic features, the cases were subdivided into 10 genetic subgroups: normal karyotype, cytogenetic failure, and eight abnormality groups. The abnormal cases were allocated to one of the cytogenetic groups in a hierarchical fashion, i.e., placed in the first applicable category (Table 1). No case was included in more than one group. The distribution of two subgroups differed significantly between the two treatment periods, with cytogenetic failures being significantly less common ($P < 0.01$) and del(9p)/*CDKN2*A deletion being significantly more common ($P < 0.001$) in the NOPHO-ALL-2000 protocol; the reason for this is the increased use of FISH analyses in the recent years. There were no significant differences between the various cytogenetic subgroups and the clinical factors gender, age, WBC count, and mediastinal/CNS involvement (data not shown).

Cytogenetic Characteristics

The cytogenetic features are summarized in Table 3. Informative karyotypic results were obtained in 249 (87%) of the 285 cases, with 119 (48%) being cytogenetically abnormal. The most frequent aberrations, as identified by chromosome banding analysis, were TCR gene rearrangements (20%; 24/119) [TCR;11p13 (10%; 12/119), TCR;10q24 (3%; 3/119), TCR;other (8%; 9/119)], del(9p) (17%; 20/119), +8 (14%; 17/119), del(6q) (12%; 14/119), and 11q23 rearrangements (6%; 7/119). The TCR;other group comprised the rare rearrangements t(X;14)(p11;q11), t(X;7)(q22;q34), t(1;14)(p32;q11), ins(14;5)(q11;q?q?), inv(7)(p15q34), t(8;14)(q24;q11), t(7;11)(q34;p15), and t(12;14)(p13;q11). Most (62%; 74/119) of the aberrant T-ALLs were pseudodiploid and close to 50% (56/119) harbored only one chromosome abnormality. Structural changes were more common than numerical ones, with 86% (102/119) and 41% (49/119) of abnormal cases displaying at least one structural or numerical anomaly, respectively. The breakpoint distribution of the structural chromosome aberrations is given in Figure 1. As seen, breakpoints cluster in the 6q2, 7q3, 9p1, 11p1, 11q2, and 14q1 chromosome regions.

Outcome in the Different Cytogenetic Subgroups

There were no significant differences in pEFS or pOS between patients with cytogenetic failures

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TABLE 1. Clinical and Cytogenetic Features of the 285 Pediatric T-Cell Acute Lymphoblastic Leukemias

Cytogenetic subgroup	No. (%)	Sex ratio (M/F)	Median age (range)	Median WBC count $\times 10^9$/l (range)	Mediastinal/CNS involvement (%)	5-year pEFS (SE)	5-year pOS (SE)
Normal	124 (44)	3.0	9.1 (0.4–17)	69 (0.5–990)[a]	76/12 (61/9.7)	0.64 (0.04)[b]	0.68 (0.04)[b]
Failure	33 (12)	3.1	8.5 (2.5–16)	63 (2.5–664)[c]	22/2 (67/6.1)[d]	0.66 (0.08)	0.69 (0.08)
Abnormal[e]	128 (45)	3.1	8.8 (0.8–17)	61 (0.8–815)	71/13 (55/10)	0.57 (0.05)[f]	0.65 (0.04)[f]
7q34-36 or 14q11	24 (8.4)	7.0	10.5 (2.3–17)	72 (1.2–443)	13/2 (54/8.3)	0.41 (0.11)	0.55 (0.11)
11p13 partner	12 (4.2)	11	10.5 (2.3–16)	135 (1.2–443)	7/1 (58/8.3)	0.49 (0.18)	0.66 (0.14)
10q24 partner	3 (1.1)	2.0	5.1 (4.5–16)	57 (13–87)	1/0 (33/0)	0.67 (0.27)	1.00 (0.00)
Other partner	9 (3.2)	8.0	11.5 (6.0–17)	18 (1.5–424)	5/1 (56/11)	0.22 (0.14)	0.30 (0.16)
11q23 rearrangement	7 (2.5)	1.3	8.8 (1.6–15)	52 (0.8–588)	2/1 (29/14)	0.57 (0.19)	0.57 (0.19)
del(9p)/*CDKN2A* deletion[g]	24 (8.4)	3.8	10.0 (2.6–16)	35 (1–332)[h]	13/5 (54/21)	0.69 (0.10)	0.82 (0.09)
del(6q)	8 (2.8)	3.0	5.8 (1.3–15)	134 (3.4–815)	7/1 (87/12)	0.62 (0.17)	0.57 (0.19)
+8 as a sole change	6 (2.1)	5.0	11.5 (5.0–17)	175 (1.4–304)	5/1 (83/17)	0.67 (0.19)	0.67 (0.19)
Other changes	59 (21)	2.5	8.0 (0.8–17)	66 (0.9–723)	31/3 (52/5.1)[i]	0.56 (0.07)[j]	0.64 (0.07)[j]
Total	285	3.1	9.0 (0.4–17)	66.5 (0.5–990)[k]	169/27 (59/9.5)[l]	0.61 (0.03)[m]	0.67 (0.03)[m]

CNS, central nervous system; F, female; M, male; pEFS, probability of event-free survival; pOS, probability of overall survival; SE, standard error; WBC, white blood cell.

[a]Inormation on WBC count missing in two cases.

[b]Based on 123 cases (one infant case was excluded).

[c]Inormation on WBC count missing in one case.

[d]Inormation on mediastinal mass missing in one case.

[e]The abnormal cases were allocated to one of the cytogenetic groups in a hierarchical fashion, i.e., placed in the first applicable category.

[f]Based on 125 cases (three infant cases were excluded).

[g]Includes all unbalanced structural rearrangements resulting in loss of 9p as well as cases identified only by FISH analyses of *CDKN2A* (n = 6).

[h]Inormation on WBC count missing in one case.

[i]Inormation on mediastinal mass and CNS involvement missing in two cases and one case, respectively.

[j]Based on 56 cases (three infant cases were excluded).

[k]Inormation on WBC count missing in four cases.

[l]Inormation on mediastinal mass and CNS involvement missing in three cases and one case, respectively.

[m]Based on 281 cases (four infant cases were excluded).

TABLE 2. The Impact of Clinical and Basic Cytogenetic Features on pEFS and pOS in 248 Pediatric T-Cell Acute Lymphoblastic Leukemias[a]

Features	pEFS (SE)	*P* value	pOS (SE)	*P* value
Clinical features				
Gender (male vs. female)	0.60 (0.04) vs. 0.61 (0.06)	0.74	0.65 (0.04) vs. 0.70 (0.06)	0.79
Age (<10 vs. ≥10 years)	0.59 (0.04) vs. 0.63 (0.05)	0.49	0.65 (0.04) vs. 0.69 (0.05)	0.46
WBC count (<200 vs. ≥200 × 10^9/l)[b]	0.67 (0.04) vs. 0.41 (0.06)	<0.001	0.73 (0.03) vs. 0.41 (0.06)	<0.001
Medistinal involvement (yes vs. no)[c]	0.63 (0.04) vs. 0.55 (0.05)	0.13	0.69 (0.04) vs. 0.64 (0.05)	0.19
CNS involvement (yes vs. no)	0.56 (0.10) vs. 0.61 (0.03)	0.24	0.63 (0.10) vs. 0.67 (0.03)	0.38
Treatment protocol (ALL-1992 vs. ALL-2000)	0.61 (0.04) vs. 0.62 (0.05)	0.75	0.67 (0.04) vs. 0.67 (0.05)	0.88
Cytogenetic feature				
Normal vs. abnormal	0.64 (0.04) vs. 0.57 (0.05)	0.19	0.68 (0.04) vs. 0.65 (0.04)	0.48

CNS, central nervous system; pEFS, probability of event-free survival (5 years); pOS, probability of overall survival (5 years); SE, standard error; WBC, white blood cell.
[a]Infants ($n = 4$) and cases without cytogenetic data ($n = 33$) were excluded from the total group of 285 cases.
[b]Information on WBC count missing in three cases.
[c]Information on mediastinal mass missing in one case.

TABLE 3. Cytogenetics of the Present and of Previous Large Series of Pediatric T-Cell Acute Lymphoblastic Leukemias

Cytogenetic features	Nordic series	Schneider et al. (2000)	Heerema et al. (1998)
Total no. of cases	249[a]	354	169
Normal karyotype	130 (52%)	153 (43%)	66 (39%)
Abnormal karyotype	119 (48%)	201 (57%)	103 (61%)
Ploidy levels[b]			
Hypodiploid (35–45 chromosomes)	13 (11%)	16 (8%)	4 (4%)
Pseudodiploid (46 chromosome)	74 (62%)	125 (62%)	80 (78%)
Hyperdiploid (47–50 chromosomes)	24 (20%)	46 (23%)	17 (17%)
>50 chromosomes	8 (7%)	14 (7%)	2 (2%)
Number of anomalies[b]			
1 anomaly	56 (47%)	–	–
2 anomalies	36 (30%)	–	–
≥3 anomalies	27 (23%)	–	–
Type of aberration[b]			
Structural only	70 (59%)	–	–
Numerical only	17 (14%)	–	–
Structural and numerical	32 (27%)	–	–
Chromosomal abnormalities[b]			
del(9p)[c]	20 (17%)	31 (15%)	15 (15%)
14q11 breakpoint	19 (16%)	44 (22%)	29 (28%)
+8	17 (14%)	22 (11%)	11 (11%)
del(6q)	14 (12%)	36 (19%)	31 (30%)
t(11;14)(p13;q11)	10 (8%)	14 (7%)	13 (13%)
7q32-36 breakpoint	8 (7%)	15 (7%)	8 (8%)
11q23 breakpoint	7 (6%)	–	9 (9%)
del(12p)	6 (5%)	9 (4%)	4 (4%)
t(10;14)(q24;q11)	3 (3%)	12 (6%)	3 (3%)

[a]Cytogenetic failures or cases with only FISH information in the Nordic series were excluded in order to compare similar data among the different series.
[b]Percentages of cytogenetically abnormal cases.
[c]Includes monosomy 9 and all unbalanced structural rearrangements resulting in loss of 9p.

and nonfailures ($P = 0.46$ and $P = 0.70$, respectively) or between cases with a normal or abnormal karyotype, as ascertained by chromosome and/or FISH analyses (Table 2). The nine cytogenetic groups (normal karyotype and the eight different abnormality subgroups; failures excluded) did not show any overall difference in pEFS ($P = 0.19$) or pOS ($P = 0.29$) (Fig. 2). However, patients in the subgroup TCR;other had a particularly dismal outcome with a pEFS of 0.22 (±0.14) and a pOS of 0.30 (±0.16) (Table 1 and Fig. 2). In a multivariate analysis, this

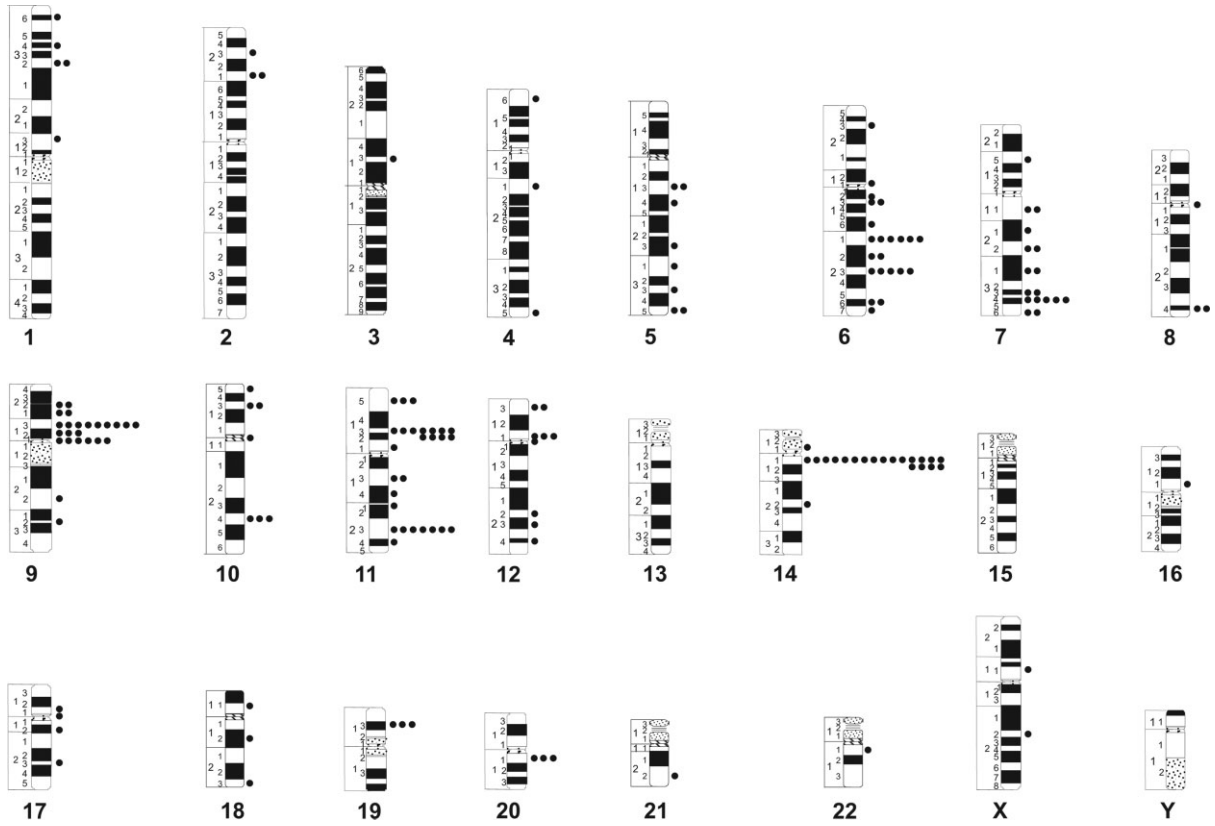

Figure 1. Ideogram displaying the breakpoint distribution in the 85 pediatric T-ALLs harboring structural chromosome aberrations with detailed breakpoint information.

subgroup had a significant impact on pEFS compared with all other cases ($P < 0.01$) as well as compared with only the cytogenetically normal subgroup ($P = 0.001$), also when adjusted for WBC count and CNS involvement (Table 4).

DISCUSSION

The salient finding in this series of 285 cytogenetically and clinically characterized T-ALLs, comprising all children and adolescents below the age of 18 years diagnosed in the Nordic countries between 1992 and 2006, was that the subgroup with rare TCR rearrangements had a significantly worse outcome than all other cases. This result, albeit based on a limited number of patients, is indirectly supported by the fact that the cytogenetic and clinical features of this population-based patient cohort agree very well those of previous large series of T-ALL (Tables 3 and 5).

Apart from the present investigation, we know of only three studies that have included at least 200 childhood T-ALLs and that have provided detailed information on clinical characteristics such as median age and WBC counts, sex distribution, CNS involvement, and outcome in relation to basic karyotypic patterns (Pullen et al., 1999; Schneider et al., 2000; Ballerini et al., 2008). As seen in Table 5, these three series are quite similar with regard to age at diagnosis, WBC counts, male/female ratio, and the incidence of extra-medullary involvement. In the Nordic cohort, we found no significant correlation between CNS involvement and outcome, in agreement with previous studies (Pui et al., 1990; Arico et al., 1995; Pullen et al., 1999). Nor did mediastinal mass, gender or age have any prognostic impact, as also previously reported by several groups (Garand et al., 1990; Arico et al., 1995; van Grotel et al., 2008). However, in the study by Pullen et al. (1999), boys fared significantly worse than girls and Pui et al. (1990) noted an increased risk of treatment failure in adolescents aged $\geq$15 years. In the present series, the only clinical factor significantly affecting outcome, also in multivariate analysis, was a WBC count of $\geq 200 \times 10^9$/l; similar associations have been found in several (Garand et al., 1990;

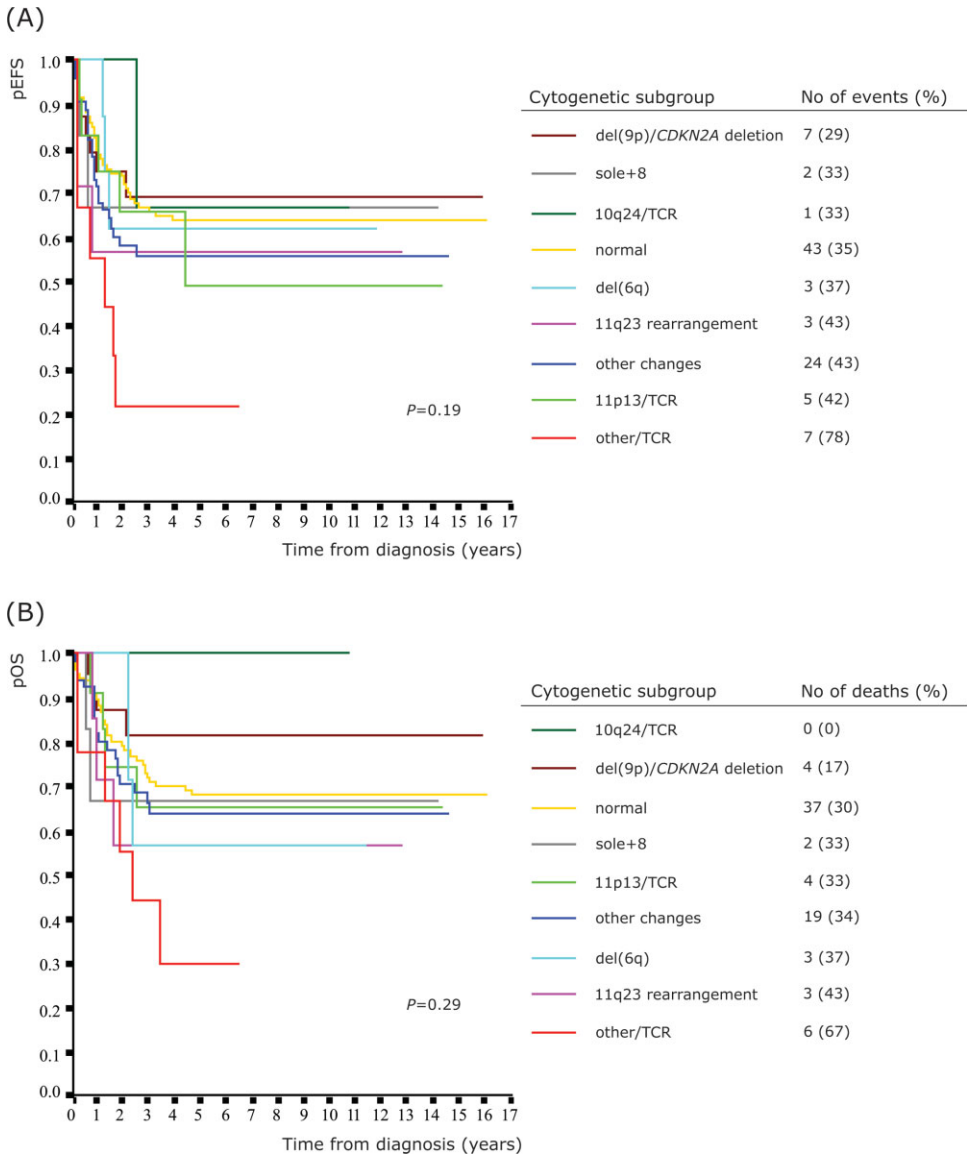

Figure 2. (A) Predicted event-free survival (pEFS) and (B) predicted overall survival (pOS) for 281 pediatric T-ALL patients divided into nine different cytogenetic subgroups. The numbers of patients in each group are given in Table 1.

Shuster et al., 1990; Aricò et al., 1995) but not all previous investigations (Pui et al., 1990; Pullen et al., 1999; Ballerini et al., 2008; van Grotel et al., 2008).

The cytogenetic patterns of the present series are also well in accordance with previous studies (Table 3), with the vast majority of the T-ALLs being pseudodiploid with one or two chromosome aberrations. The most frequent changes were TCR gene rearrangements and del(9p) (Table 3). Among the various TCR translocations, t(11;14)(p13;q11) was the most common, as also seen in previous studies (Heerema et al., 1998; Schneider et al., 2000). The latter group reported that t(11;14)(p13;q11)-positive cases were characterized by high median WBC counts and possibly by young age. We could not confirm the association with age, but the median WBC count was clearly higher than the median value for the entire cohort (Table 1). The t(10;14)(q24;q11) was less frequent than t(11;14)(p13;q11) in this Nordic series, which is in line with other investigations (Heerema et al., 1998; Schneider et al., 2000; Van Vlierberghe et al., 2006; Bergeron et al., 2007; Ballerini et al., 2008) (Table 3). The TCR;other group was cytogenetically very

TABLE 4. Multivariate Analysis Using the Cox Regression Model for 248 Pediatric T-Cell Acute Lymphoblastic Leukemias[a]

Parameters	Unadjusted *P* value[b]	HR	CI (95%)	Adjusted *P* value	HR	CI (95%)
Cytogenetic subgroup						
Normal	Reference	1.00	–	–	1.00	–
TCR	0.067	1.788	0.961–3.329	0.007	2.452	1.285–4.680
11p13 partner	0.650	1.239	0.491–3.130	0.420	1.467	0.578–3.727
10q24 partner	0.814	0.788	0.109–5.728	0.932	1.091	0.149–8.008
Other partner	0.003	3.367	1.511–7.502	0.001	3.789	1.692–8.487
11q23 rearrangement	0.517	1.472	0.457–4.746	0.773	1.188	0.367–3.842
del(9p)/*CDKN2A* deletion[c]	0.803	0.903	0.406–2.008	0.875	1.067	0.475–2.398
del(6q)	0.970	1.023	0.317–3.297	0.699	0.792	0.243–2.582
+8 as a sole change	0.988	1.011	0.245–4.174	0.937	0.944	0.228–3.904
Other changes	0.220	1.367	0.829–2.254	0.156	1.437	0.871–2.370
WBC count (<200 vs. ≥200 x 10^9/l)[d]	–	–	–	<0.001	2.299	1.509–3.502
CNS involvement	–	–	–	0.155	1.592	0.839–3.024

CI, confidence interval; CNS, central nervous system; HR, hazard ratio; WBC, white blood cell.
[a]Cases without cytogenetic data ($n = 33$) or infants ($n = 4$) were excluded from the total cohort of 285 patients.
[b]Not including WBC count and CNS involvement.
[c]Includes also cases identified only by FISH analyses of *CDKN2A* ($n = 6$).
[d]Information on WBC count missing in three cases.

TABLE 5. Clinical Features of the Present and of Previous Large Series of Pediatric T-Cell Acute Lymphoblastic Leukemias

Clinical features	Nordic series	Ballerini et al. (2008)	Schneider et al. (2000)	Pullen et al. (1999)
Total no. of patients	285	200	354	441
Age (median years)	9.0	9.1	8.2	8.2
WBC count $\times 10^9$/l (median)	66	99	70	75
Sex ratio (M/F)	3.1	2.3	3.0	3.0
CNS involvement (%)	9.5	–	–	11
Mediastinal involvement (%)	59	70	–	–
pEFS (all cases)	0.61	0.58	–	0.51
pEFS (normal karyotype)	0.64	–	0.62	–
pEFS (abnormal karyotype)	0.57	–	0.51	–
pOS (all cases)	0.67	0.62	–	–

CNS, central nervous system; F, female; M, male; pEFS, probability of event-free survival (5 years); pOS, probability of overall survival (5 years); WBC, white blood cell.

TABLE 6. The Nine Pediatric T-Cell Acute Lymphoblastic Leukemias with Rare TCR Rearrangements

Rearrangement	Age/sex	WBC count ($\times 10^9$/l)	Mediastinal/CNS involvement	Survival (months)	No. of published cases[a]	Target gene
t(X;14)(p11;q11)	13/M	12	Yes/yes	1.1	0	Unknown
t(X;7)(q22;q34)	12/M	4.9	No/no	28.3	1[b]	*IRS4* (Karrman et al., 2009)
t(1;14)(p32;q11)	16/M	12	Yes/no	51.3+	10	*TAL1* (Finger et al., 1989)
ins(14;5)(q11;q?q?)	9/M	264	Yes/no	77.6+	0	Unknown
inv(7)(p15q34)	11/M	1.5	No/no	41.0	3	*HOXA* (Speleman et al., 2005)
t(8;14)(q24;q11)	6/M	264	No/no	22.3	19	*MYC* (Erikson et al., 1986)
t(8;14)(q24;q11)	6/M	197	No/no	1.5	19	*MYC* (Erikson et al., 1986)
t(7;11)(q34;p15)	8/M	4.9	Yes/no	31.5+	2	*LMO1* (Cauwelier et al., 2006)
t(12;14)(p13;q11)	14/F	424	Yes/no	15.4	3[c]	*CCND2* (Karrman et al., 2006)

CNS, central nervous system; F, female; M, male; WBC, white blood cell; +, alive at last follow-up.
[a]Based on pediatric T-ALL cases included in the Mitelman Database of Chromosome Aberrations in Cancer (Mitelman et al., 2009).
[b]Same case as in the present series.
[c]Includes the case in the present series.

heterogeneous, comprising eight different TCR rearrangements, with only the t(8;14)(q24;q11) being recurrent (Table 6). However, when taking literature data into account (Mitelman et al., 2009), also t(1;14)(p32;q11), inv(7)(p15q34), t(7;11)(q34;p15), and t(12;14)(p13;q11) are recurrent (Table 6). Loss of 9p material was seen in close to 20% of the cytogenetically abnormal

TABLE 7. Associations Between Cytogenetic Subgroups and Outcome in Pediatric T-Cell Acute Lymphoblastic Leukemias

Cytogenetic subgroup	pEFS/pOS in the present series	Outcome in previous series	Reference
TCR			
11p13/*LMO2*	0.49/0.66	Undefined	Van Vlierberghe et al. (2008)
10q24/*TLX1*	0.67/1.00	Good	Schneider et al. (2000), Cavé et al. (2004), Bergeron et al. (2007)
Other partner	0.22/0.30	Undefined	
t(X;14)(p11;q11)	NA	Undefined	
t(X;7)(q22;q34)	NA	Undefined	
t(1;14)(p32;q11)	NA	Good	Cavé et al. (2004), van Grotel et al. (2008)
ins(14;5)(q11;q?q?)	NA	Undefined	
inv(7)(p15q34)	NA	Undefined	Cauwelier et al. (2007), Van Vlierberghe et al. (2008)
t(8;14)(q24;q11)	NA	Undefined	
t(7;11)(q34;p15)	NA	Undefined	Van Vlierberghe et al. (2008)
t(12;14)(p13;q11)	NA	Undefined/poor	Karrman et al. (2006)
11q23/*MLL* rearrangement	0.57/0.57	Undefined	Graux et al. (2006)
t(11;19)(q23;p13.3)/*MLL-MLLT1*	1.00/1.00	Good	Huret et al. (1993), Rubnitz et al. (1999), Graux et al. (2006)
del(9p)/*CDKN2A* deletion	0.69/0.82	Undefined/poor	Ramakers-van Woerden et al. (2001), Van Vlierberghe et al. (2008)
del(6q)	0.62/0.57	Undefined	Heerema et al. (2000)
+8	0.67/0.67	Undefined	Heerema et al. (1998), Schneider et al. (2000)

NA, not applicable (too few cases for statistical analysis; see Table 6); pEFS, probability of event-free survival (5 years); pOS, probability of overall survival (5 years).

cases (Table 3). This is clearly an underestimate since the observed frequency was based on G-banding alone and targeted FISH analyses of *CDKN2A* in other studies have shown hemi- or homozygous deletions of this gene in 70–80% of T-ALLs (Ramakers-van Woerden et al., 2001; Bertin et al., 2003; Graux et al., 2006; Van Vlierberghe et al., 2008).

In this Nordic series, there were no significant differences in outcome between cytogenetic failures and nonfailures or between cases with a normal or abnormal karyotype (Table 2) nor was there any overall significant difference within the entire cytogenetically informative group (Fig. 2). No specific abnormalities, with the exception of the TCR;other group, were associated with an increased risk of therapy failure (Fig. 2 and Tables 1 and 4). This is in line with findings in several previous studies (Table 7). However, some aberrations have been proposed to confer either a poor or good outcome. For example, several investigators have suggested that the t(10;14)(q24;q11)/*TLX1* activation is associated with a favorable prognosis (Schneider et al., 2000; Cavé et al., 2004; Bergeron et al., 2007). The low number of t(10;14)-positive cases in the present series ($n = 3$) precludes any clear-cut conclusions, but it is noteworthy that all patients are alive 40, 97, and 129 months after diagnosis. The t(11;19)(q23;p13.3)/*MLL-MLLT1* has also been correlated with a favorable outcome (Huret et al., 1993; Rubnitz et al., 1999; Graux et al., 2006), and again all three Nordic patients with this translocation are alive 36, 71, and 154 months after diagnosis and none of them has had an event.

The only cytogenetic finding negatively affecting EFS was the presence of rare TCR rearrangements (Table 4). Cases with such changes had more than twice as many events, including deaths, compared with all other patients. It is noteworthy that this cytogenetic group displayed a relatively low median WBC count (18×10^9/l) and that there was no overrepresentation of extramedullary involvement (Table 1). Thus, this group was not characterized by any classical high-risk criteria that would predict an adverse outcome. However, it should be emphasized that the group is small as well as genetically very heterogeneous (Table 6). Hence, the poor outcome might not apply for all rare TCR rearrangements. In fact, the t(1;14)(p32;q11)/*TAL1* activation has previously been suggested to have a favorable impact on prognosis (Cavé et al., 2004; van Grotel et al., (2008), and our only patient with this translocation is alive, without any events, more than 50 months after diagnosis (Table 6). This notwithstanding and considering the clinically important ramifications of a poor prognostic impact of

rare TCR rearrangements, not least taking into account the absence of risk-stratifying clinical features, it is crucial that this preliminary finding is addressed in further studies. Because the aberrations are individually quite rare (Table 6), collaborative efforts will be needed to provide conclusive results that can be used in future treatment protocols.

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