Additional aberrations of the ETV6 and RUNX1 genes have no prognostic impact in 229 t(12;21)(p13;q22)-positive B-cell precursor acute lymphoblastic leukaemias treated according to the NOPHO-ALL-2000 protocol

The ETV6/RUNX1 fusion, which is the molecular consequence of the cytogenetically cryptic t(12;21)(p13;q22), is present in approximately 25% of paediatric B-cell precursor acute lymphoblastic leukaemia (BCP ALL) cases in the Nordic countries. ETV6/RUNX1-positive BCP ALL is generally considered to have an excellent prognosis; however, reports of frequent late relapses as well as similar incidences of t(12;21) in newly diagnosed and relapsed cases have cast doubts on its favourable prognostic impact [1–3]. Furthermore, the clinical consequences of additional aberrations involving the ETV6 and RUNX1 genes, e.g., deletions of wild-type ETV6 and trisomy 21, harbouring either a non-rearranged RUNX1 gene or an additional ETV6/RUNX1 chimaera, have also been debated. For example, 12p deletions, involving the non-rearranged ETV6 allele, have been suggested to influence adversely the outcome [4]. In addition, Stams et al. reported that the subgroups with either an additional ETV6/RUNX1 fusion gene, located on an extra del(21)t(12;21), or without any secondary aberration involving the ETV6 and RUNX1 genes did worse in terms of disease-free survival [5]. Furthermore, the frequencies of additional aberrations of these genes, with the exception of ETV6 deletions, have been shown to be higher in relapsed than in diagnostic samples [6]. On the other hand, in a large study comprising 245 t(12;21)-positive cases, the presence of secondary aberrations of 12p and 21q did not predict a higher risk of relapse [7], and, recently, cases with ETV6 deletions were actually shown to have a more favourable prognosis than cases without deletions [8]. In order to address this potentially clinically important issue we have ascertained and reviewed all ETV6/RUNX1-positive cases treated according to the NOPHO-ALL-2000 protocol.

All fluorescence in situ hybridisation (FISH)-verified ETV6/RUNX1-positive BCP ALL cases in children aged 1–15 years diagnosed in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) between January 2000 and December 2008 and treated according to the NOPHO-ALL-2000 protocol were included in the present study. Among the 1001 BCP ALL cases diagnosed during this time period and analysed as regards the presence of t(12;21) by FISH and/or reverse transcription-polymerase chain reaction analyses, the ETV6/RUNX1 fusion was detected in 242 (24%) cases, of which 229 (95%) had been analysed by FISH. Only the latter are included in the present study because they are the ones informative regarding additional ETV6 and/or RUNX1 abnormalities. The FISH patterns ascertained were: (i) t(12;21) alone; (ii) loss of wild-type ETV6 (“del(ETV6)”); (iii) additional ETV6/RUNX1 fusion (“+der(21)t(12;21)”), (iv), gain of RUNX1 (“+21”), and (v) combinations of del(ETV6), +21, and +der(21)t(12;21). In total, additional changes involving the ETV6 and/or RUNX1 genes were detected in 131 (57%) of the 229 cases, with deletion of ETV6 being most common (38%). The majority (86%) harboured only one additional aberration, whereas 14% had two or more secondary changes. The incidence of secondary aberrations in the present series is lower than the approximately 75–80% reported in some previous studies [4,5,7]. Whether this difference is fortuitous or reflects technical and/or geographic differences is presently unknown.

The clinical characteristics at presentation, risk stratification, and probabilities of event-free and overall survival (pEFS and pOS) for the entire patient cohort (n = 229) as well as for the five different genetic subgroups are listed in Table 1. There were no significant differences among the subgroups as regards white blood cell counts, age, and risk stratification. A total of 29 events (26 relapses, two second malignant neoplasms, and one induction failure) occurred during the observation period, with the median time to relapse being 36 months (range 20–86 months). Among the cases that relapsed, 14 (54%) had additional ETV6 and/or RUNX1 aberrations at diagnosis, a proportion similar to the one for the whole cohort (57%) indicating that cases with such secondary aberrations are not more likely to relapse. Patients with trisomy 21 had the highest frequency (17%) of relapses; however, the distributions of genetic subgroups among the children that relapsed and the whole cohort did not differ significantly. Neither pEFS nor pOS varied significantly among the five genetic subgroups (Fig. 1 and Table 1). Thus, in agreement with the findings in another large series of t(12;21)-positive cases [7] we found no evidence for any

<table>
<thead>
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<th>Table 1</th>
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<td>Clinical features and risk groups of the 229 t(12;21)-positive BCP ALL cases.</td>
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<th>Genetic subgroup</th>
<th>Median WBC × 10^9/l (range)</th>
<th>Median age (range)</th>
<th>Risk group (SR/IR/HR in %)</th>
<th>Relapses (%)</th>
<th>pEFS (SE)</th>
<th>pOS (SE)</th>
</tr>
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<tbody>
<tr>
<td>t(12;21) only (n = 98; 43%)</td>
<td>8.0 (0.8–164)</td>
<td>4.8 (1.4–16)</td>
<td>38/39/23</td>
<td>12 (12)</td>
<td>0.80 (0.06)</td>
<td>0.89 (0.05)</td>
</tr>
<tr>
<td>del(ETV6) (n = 69; 30%)</td>
<td>5.0 (0.2–160)</td>
<td>3.6 (1.4–15)</td>
<td>42/42/16</td>
<td>6 (8.7)</td>
<td>0.89 (0.04)</td>
<td>0.97 (0.02)</td>
</tr>
<tr>
<td>+der(21)t(12;21) (n = 26; 11%)</td>
<td>5.2 (1.2–194)</td>
<td>5.0 (1.7–11)</td>
<td>54/27/19</td>
<td>3 (12)</td>
<td>0.86 (0.08)</td>
<td>1.0 (0.00)</td>
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<tr>
<td>n = 18; 7.9%</td>
<td>4.9 (1.9–225)</td>
<td>3.9 (2.5–10)</td>
<td>50/34/16</td>
<td>3 (17)</td>
<td>0.81 (0.10)</td>
<td>0.88 (0.12)</td>
</tr>
<tr>
<td>+21 (n = 18; 7.9%)</td>
<td>3.6 (1.1–100)</td>
<td>4.3 (1.8–11)</td>
<td>45/33/22</td>
<td>2 (11)</td>
<td>0.74 (0.15)</td>
<td>0.94 (0.05)</td>
</tr>
<tr>
<td>Combined cohort (n = 229; 100%)</td>
<td>5.5 (0.2–225)</td>
<td>4.7 (1.4–16)</td>
<td>42/38/20</td>
<td>26 (11)</td>
<td>0.82 (0.04)</td>
<td>0.93 (0.03)</td>
</tr>
</tbody>
</table>

BCP ALL, B-cell precursor acute lymphoblastic leukaemia; HR, high risk; IR, intermediate risk; pEFS, probability of event-free survival; pOS, probability of overall survival; SE, standard error; SR, standard risk; WBC, white blood cell count.

0145-2126/5 – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.leukres.2012.03.024
prognostic impact of additional ETV6 and/or RUNX1 abnormalities in this cytogenetic BCP ALL subtype.

Conflicts of interest

The authors declare no potential conflicts of interest.

Acknowledgements

The authors are grateful to all the members of the NOPHO society that contributed cytogenetic and clinical data. This study was supported by grants from the Swedish Childhood Cancer Foundation, Karolinska Institutet, and the Stockholm County Health Care System. G.B. analysed the data and wrote the manuscript; M.K.A., K.A., Ge.B., L.C., I.G., S.H., K.H., R.H., J.H.J., E.K., A.N., and L.P. contributed data; B.J. and E.F. designed the study and wrote the manuscript. All authors critically reviewed the manuscript and approved the final version.

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16 January 2012
Available online 21 April 2012