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Paediatric B-cell precursor acute lymphoblastic leukaemia with t(1;19)(q23;p13): clinical and cytogenetic characteristics of 47 cases from the Nordic countries treated according to NOPHO protocols

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Summary

The translocation t(1;19)(q23;p13)/der(19)t(1;19) is a risk stratifying aberration in childhood B-cell precursor acute lymphoblastic leukaemia (BCP ALL) in the Nordic countries. We have identified 47 children/adolescents with t(1;19)/der(19)t(1;19)-positive BCP ALL treated on two successive Nordic Society of Paediatric Haematology and Oncology (NOPHO) protocols between 1992 and 2007 and have reviewed the clinical and cytogenetic characteristics of these cases, comprising 1·8% of all cases. The translocation was balanced in 15 cases (32%) and unbalanced in 29 cases (62%). The most common additional chromosome abnormalities were del(9p), i(9q), del(6q), and del(13q). The median age was 7 years, the median white blood cell (WBC) count was 16×10^9/l, and the female/male ratio was 1·2. The predicted event-free survival (EFS) at 5 and 10 years was 0·79, whereas the predicted overall survival (OS) at 5 and 10 years was 0·85 and 0·82, respectively. Nine patients had a bone marrow relapse after a median of 23 months; no patient had a central nervous system relapse. Additional cytogenetic abnormalities, age, gender, WBC count or whether the t(1;19) was balanced or unbalanced did not influence EFS or OS. Compared to cases with t(12,21) and high hyperdiploidy, EFS was similar, but overall survival was worse in patients with t(1;19)/der(19)t(1;19) ($P = 0·004$).

Keywords: acute lymphoblastic leukaemia, paediatric, t(1;19), *TCF3*, *PBX1*.

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The translocation t(1;19)(q23;p13), and its unbalanced variant der(19)t(1;19)(q23;p13), is a primary and well known chromosome abnormality in childhood B-cell precursor acute lymphoblastic leukaemia (BCP ALL), being present in 3–5% of all such cases (Raimondi *et al*, 1990; Pui *et al*, 1994; Hunger, 1996; Uckun *et al*, 1998; Forestier *et al*, 2008a; Moorman *et al*, 2010; Schmiegelow *et al*, 2010). In contrast to some paediatric ALL-associated abnormalities, such as high hyperdiploidy, t(12;21)(p13;q22), and *MLL* rearrangements (Gale *et al*, 1997; Wiemels *et al*, 1999; Taub *et al*, 2002), the t(1;19)/der(19)t(1;19) does not seem to arise *in utero* (Wiemels *et al*, 2002); nor does t(1;19)/der(19)t(1;19)-positive BCP ALL display the typical 'age peak' seen in childhood leukaemias with high hyperdiploidy, t(12;21) or dic(9;20)(p13;q11) (Forestier & Schmiegelow, 2006; Forestier *et al*, 2008b). Both the balanced and the unbalanced t(1;19) results in the fusion of *TCF3* on 19p13 with *PBX1* on 1q23 (Mellentin *et al*, 1989), with the *TCF3-PBX1* fusion transcript being expressed from the derivative chromosome 19. The fusion protein consists of the transactivating domain of TCF3 and the DNA binding domain of the homeobox protein PBX1, converting PBX1 into a transactivating factor. In addition, the fusion protein appears to have a dominant negative effect on the wildtype TCF3 activity. So both increased expression of PBX1 target genes and reduction in *TCF3* activity are thought to be important in leukaemogenesis (reviewed in Aspland *et al*, 2001).

Initially, t(1;19) was associated with a poor prognosis in BCP ALL (Crist *et al*, 1990; Secker-Walker *et al*, 1992; Uckun *et al*, 1998), but a gradual intensification of treatment over time has, to some extent, circumvented the inferior outcome previously associated with this translocation (Pui *et al*, 2010; Schmiegelow *et al*, 2010). For this reason, *TCF3-PBX1* is no longer risk stratifying in most contemporary treatment protocols; however, it still stratifies for intensified treatment in the Nordic countries and at the St Jude Children's Research Hospital (Pui *et al*, 2010; Schmiegelow *et al*, 2010). Support, albeit indirect, for the latter comes from a recent study reporting an increased risk for central nervous system (CNS) relapse in paediatric t(1;19)/der(19)t(1;19)-positive BCP ALL (Jeha *et al*, 2009). Furthermore, data are still conflicting as regards whether the balanced t(1;19) confers a worse prognostic impact than does the unbalanced der(19) and whether additional cytogenetic abnormalities influence the outcome (Secker-Walker *et al*, 1992; Uckun *et al*, 1998; Sharma *et al*, 2001; Kager *et al*, 2007; Jeha *et al*, 2009). In order to address these issues, we have ascertained and reviewed the clinical and cytogenetic characteristics of all children/adolescents with BCP ALL and t(1;19) diagnosed between 1992 and 2007 in the Nordic countries and treated according to two consecutive NOPHO protocols.

Patients and methods

Patient selection and genetic analyses

Between January 1, 1992 and December 31, 2007, 2640 infants, children, and adolescents (0–18 years) were diagnosed with BCP ALL in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). During this time period, two different protocols were used (NOPHO-ALL-1992 and NOPHO-ALL-2000) (Gustafsson *et al*, 2000; Schmiegelow *et al*, 2010). These protocols were closely related and comparable with respect to therapy. In both protocols, t(1;19)/der(19)t(1;19) was a risk stratifying aberration, assigning patients to intensive therapy. The risk groups and the main treatment features of both protocols are discussed in Schmiegelow *et al* (2010). Both NOPHO protocols were approved by the local scientific ethical committees, and parents gave informed consent to enrolment of their children in the protocols.

Chromosome banding analyses were performed using standard methods in 15 cytogenetic laboratories in the Nordic countries. All abnormal karyotypes have been centrally reviewed annually in Sweden since 1996 and in all five Nordic countries since 2000. All cases with t(1;19) or der(19)t(1;19) detected by chromosome banding were included in the study; in recent years, most cases have also been verified by fluorescence *in situ* hybridization (FISH) and/or reverse transcription-polymerase chain reaction (RT-PCR) analyses. Cases without a successful karyotype were also included if positive by FISH for *TCF3* rearrangements and/or RT-PCR for the *TCF3-PBX1* fusion (van Dongen *et al*, 1999). The cytogenetic characteristics ascertained were type of t(1;19) (balanced or unbalanced), modal chromosome number (only the most basic clone and the lowest mode in cases with modal number variations), and incidence and types of cytogenetic changes in addition to t(1;19).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software 11.0 for Macintosh was used for the statistical analyses (SPSS, Chicago IL, USA). The probability of event-free survival (EFS) was calculated using the Kaplan–Meier method. In the analysis of EFS, events comprised induction failures, death in remission, relapse, and the occurrence of a second malignancy. In overall survival (OS), death was the end-point. Patients in first complete remission were followed between 38 and 203 months (median 104 months). Last date of follow-up was February 11, 2011.

Results

Patients and basic cytogenetic/patient data

The t(1;19)/der(19)t(1;19) and/or *TCF3* rearrangement/*TCF3-PBX1* fusion was identified in 47 (1·8%) of 2640 infants, children, and adolescents diagnosed with BCP ALL in the Nordic countries between 1992 and 2007 (the frequencies were 1·0% and 3·0% in the 1992 and 2000 protocols, respectively). Chromosome banding only was performed in 17 cases, chromosome banding combined with FISH and/or RT-PCR were performed in 27 cases, and FISH and/or RT-PCR only

were, due to karyotypic failure, performed in three cases. Conflicting results between G-banding, FISH and RT-PCR was noted in three cases (Cases 7, 22, and 32; Table I). One (Case 32) was positive by G-banding analysis and FISH for *TCF3* rearrangement, but was negative by RT-PCR for *TCF3-PBX1*, whereas two cases (Cases 7 and 22) displayed a typical t(1;19)(q23;p13) or der(19)t(1;19)(q23;p13) by G-banding but were RT-PCR negative for the *TCF3-PBX1* fusion.

Seventeen patients were treated according to the NOPHO-ALL-1992 protocol, whereas 30 patients were treated according to the NOPHO-ALL-2000 protocol. In the 1992 protocol, three patients (incorrectly) received standard risk therapy, eight patients received intermediate risk therapy, and six patients received high-risk therapy. In the 2000 protocol, one patient (incorrectly) received intermediate intensity therapy and 29 patients received high-risk therapy.

The median age of the patients was 7 years (range 1–18 years), and 26 were females and 21 males (female/male ratio 1·2). At the time of diagnosis, one patient had CNS involvement; no patient had mediastinal or testicular leukaemia. The median white blood cell (WBC) count was 16×10^9/l (range 1·3–159).

Cytogenetic characteristics

The translocation was balanced in 15 cases (32%) and unbalanced in 29 cases (62%); in the three cases (6%) with karyotypic failure but positive by RT-PCR it is unknown whether it was balanced or unbalanced (Table I). No case harboured both a balanced and an unbalanced translocation. There was no statistical difference in age, WBC or sex between patients with balanced and unbalanced translocations.

Of the 44 cases with an informative karyotype, 17 (39%) had no additional cytogenetic abnormalities, 17 (39%) had 1–2 additional abnormalities, five (11%) had 3–4 additional abnormalities and five (11%) had 5–9 additional abnormalities (Table I). Six (40%) out of 15 cases with a balanced t(1;19) had additional cytogenetic abnormalities, whereas 21 (72%) out of 29 cases with an unbalanced t(1;19) had additional abnormalities. This difference, however, was not statistically significant ($P = 0·5$).

The most common secondary structural abnormalities were del(9p), i(9q), del(6q), and del(13q) (Table I and Fig 1). Three of eight cases with del(9p) was identified only by FISH, using a probe for *CDKN2A*, and two additional cases had 9p deletions as a result of unbalanced translocations. Given that i(9q), found in five cases, also result in loss of 9p material, a total of 15 cases (34%) displayed 9p losses. Among the 44 cytogenetically informative cases, a modal number of 46 was observed in 33 (75%), a modal number of 45 or below in three (7%), a modal number of 47 in six (14%), and a modal number above 50 in two (5%) cases. The following numerical changes were recurrent: trisomy 4, 5, 6, 14, 17, 18, 21, 22 and tetrasomy 21 (Fig 1).

Survival

The predicted EFS at 5 as well as 10 years for the 47 patients was 0·79 (standard error, SE 0·06) (Fig 2A). There was no difference in EFS between the NOPHO-ALL-1992, and NOPHO-ALL-2000 protocols ($P = 0·6$). At last follow-up, a total of 10 events had occurred: one patient died in first complete remission at day 48 of pancreatitis, and nine patients had a bone marrow relapse after 11–42 months (median 23 months). No patients had CNS involvement as part of the first relapse, but one patient had a second relapse with combined bone marrow and CNS involvement.

The predicted OS at 5 and 10 years was 0·85 (SE 0·06) and 0·82 (SE 0·06), respectively (Fig 2B). There was no difference in OS survival between the two protocols ($P = 0·3$). Eight patients died after a median of 25 months (range 1·5–71 months). Five patients died from leukaemia (two in first relapse and three in second relapse) and three patients died in remission: one of pancreatitis (as mentioned above), one in third complete remission due to organ failure related to chronic graft-*versus*-host disease after SCT, and one in second complete remission because of haemolytic uraemic syndrome.

As a subset of t(1;19) cases do not have the *TCF3-PBX1* fusion (Privitera *et al*, 1992) it could be argued that the two RT-PCR negative cases (Cases 7 and 22) and the two hyperdiploid cases (Cases 43 and 44) should be excluded from the survival analyses. If doing so, it results in similar EFS and OS compared to the whole cohort (an EFS of 0·77 (SE 0·06) at 5 and 10 years, and an OS of 0·84 (SE 0·06) and 0·80 (SE 0·06) at 5 and 10 years, respectively).

When comparing t(1;19)/der(19)t(1;19) postive cases to cases with t(12;21) and high hyperdiploidy (HeH) from the same cohort EFS at 5 and 10 years were similar, but OS was worse ($P = 0·004$, Table II).

There was no statistically significant difference in EFS or OS between patients with balanced or unbalanced translocations ($P = 0·3$ and 0·6, respectively, Table III) or between patients with or without additional cytogenetic abnormalities ($P = 0·7$ and 0·9, respectively, Table III). Furthermore, gender, age, and WBC count had no significant impact on EFS or OS (Table III).

Discussion

The t(1;19)(q23;p13·3) was identified in 47 (1·8%) out of 2640 children diagnosed with BCP ALL in the Nordic countries between 1992 and 2007. As three of our patients with t(1;19) were negative for the *TCF3-PBX1* fusion by RT-PCR, it may be argued that they should be excluded from the cohort. This discrepancy between karyotype and molecular analysis, however, may be due to an alternative *TCF3-PBX1* fusion transcript that is undetectable by RT-PCR using standard primers for *TCF3* and *PBX1*, as reported by Paulsson *et al* (2007). Furthermore, one of these three cases was also analysed by FISH, which revealed a *TCF3* rearrangement. Hence, we believe

Table I. Age and karyotypes of 47 patients with BCP ALL and t(1;19) or der(19)t(1;19) in the Nordic countries.

Case no.	Age (years/sex)	Karyotype	FISH/RT-PCR status
1	18/F	46,XX,t(1;19)(q23;p13)	n.d.
2	8/F	46,XX,t(1;19)(q23;p13)[24]/46,XX[3]	n.d.
3	1/F	46,XX,t(1;19)(q23;p13)[7]/46,XX[18]	n.d.
4	6/F	46,XX,t(1;19)(q23;p13)[7]/46,XX[8]	n.d.
5	14/M	46,XY,t(1;19)(q23;p13)[17]/46,XY[13]	n.d.
6	1/F	46,XX,t(1;19)(q23;p13)[6]/46,XX[14]	n.d.
7	13/M	46,XY,t(1;19)(q23;p13)[11]/46,XY[4]	RT-PCR−
8	7/M	46,XY,t(1;19)(q23;p13)[9]/46,XY[3]	RT-PCR+
9	3/F	46,XX,t(1;19)(q23;p13)[4]/46,XX[20]	RT-PCR+
10	4/M	46,XY,t(1;19)(q23;p13)[3]/46,idem,del(9)(p21)[5]/46,XY[2]	n.d.
11	2/M	46,XY,t(1;19)(q23;p13)[14]/46,idem,del(9)(p21)[13]/46,XY[1]	FISH+, RT-PCR+
12	15/F	46,XX,t(1;19)(q23;p13),der(9)t(9;9)(p24;q22)	FISH+
13	13/F	46,XX,t(1;19)(q23;p13),del(9)(p21)[15]/46,idem,t(8;9)(p11;q11)[10]	RT-PCR+
14	3/F	47,XX,t(1;19)(q23;p13),?del(3)(p22p24),+21[3]46,XX[7]	n.d.
15	13/F	45,X,-X,t(1;19)(q23;p13)[3]/46,XX,t(1;19),-4,-8,-13,inc[cp17].ish.del(9)(p21p21)	FISH+
16	3/F	46,XX,der(19)t(1;19)(q23;p13)	n.d.
17	1/M	46,XY,der(19)t(1;19)(q23;p13)	FISH+
18	4/F	46,XX,der(19)t(1;19)(q23;p13)	RT-PCR+
19*	14/M	46,XY,der(19)t(1;19)(q23;p13)[6]/46,XY[20]	RT-PCR+
20	8/M	46,XY,der(19)t(1;19)(q23;p13)[6]/46,XY[19]	n.d.
21	11/F	46,XX,der(19)t(1;19)(q23;p13)[5]/46,XX[2]	n.d.
22	1/F	46,XX,der(19)t(1;19)(q23;p13)[3]/46,XX[25]	RT-PCR−
23	10/M	46,XY,der(19)t(1;19)(q23;p13)[22]/46,XY[3]	FISH+
24	3/F	46,XX,der(19)t(1;19)(q23;p13)[2]/46,XX[26].ish.+4	RT-PCR+
25	4/F	46,XX,t(5;12)(q1?3;p1?2),der(19)t(1;19)(q23;p13)[10]/46,XX[6]	FISH+
26	11/F	46,XX,del(9)(p1?3),der(19)t(1;19)(q23;q13)[6]/46,XX[4]	FISH+
27	3/F	47,XXXc,der(19)t(1;19)(q23;p13)/47,XXXc/ish.del(9)(p21p21)	RT-PCR+
28	10/M	46,XY,i(9)(q10),der(19)t(1;19)(q23;p13)[19]/46,XY[8]	FISH+
29	8/F	43–46,XX,der(19)t(1;19)(q23;p13),+mar[cp8]/46,XX[2]	RT-PCR+
30	14/F	46,XX,del(3)(q26),add(9)(p21),der(19)t(1;19)(q23;p13)	n.d.
31	18/M	47,XY,+6,i(9)(q10),der(19)t(1;19)(q23;p13)[2]/46,XY[15]	FISH+
32	11/M	46,XY,del(6)(q13q21),der(19)t(1;19)(q23;p13),der(21)t(1;21)(q21;p11)[7]/46,XY[3]	FISH+, RT-PCR−
33	4/F	46,XX,der(19)t(1;19)(q23;p13)[5]/47,idem,+22[17]/46,XX[4].ish.del(9)(p)(p21p21)	FISH+
34	8/F	46,XX,der(19)t(1;19)(q23;p13)[6]/48,XX,+21,+22[2]	FISH+
35	11/F	46,XX,der(19)t(1;19)(q23;p13][5]/46,idem,del(13)(q12q14)[12]/47,idem,del(13),+mar[3]/46,XX[4]	RT-PCR+
36	16/M	47,XY,+1,del(6)(q?),der(19)t(1;19)(q23;p13)[2]/46,idem,-1,i(9)(q10)[6]/46,XY[24]	FISH+
37	4/M	46,XY,i(7)(q10),der(19)t(1;19)(q23;p13)[2]/46–48,idem,+5,i(9)(q10)[cp3]	n.d.
38	4/M	46,XY,del(13)(q12q14),der(19)t(1;19)(q23;p13)[12]/46,idem,del(6)(q13)[3]/45–47,idem,-13,+mar[cp6]/46,XY[4]	RT-PCR+
39	7/M	46,XY,der(19)t(1;19)(q23;p13)/49,idem,+4,+5,+8,inv(13)(q?)/46,XY	n.d.
40	11/F	35–47,XX,add(1)(p11),add(5)(q22),add(6)(q13),del(9)(p22),der(19)t(1;19)(q23;p13)[cp13]	RT-PCR+
41*	3/M	47,XY,+i(1)(q10),del(13)(q21),der(19)t(1;19)(q23;p13)[14]/46,XY,del(6)(q22),der(12)del(12)(p11)add(12)(q21),del(13),der(19)t(1;19)[7]/46,XX[2]	RT-PCR+
42	12/M	46,XY,-6,-7,i(9)(q10),der(19)t(1;19)(q23;p13),+2mar,inc	n.d.
43	6/F	56–57,XX,der(19)t(1;19)(q23;p13),+6,+10,+14,+17,+18,+21,+21+mar,inc	n.d.
44	6/M	53–57,XY,+X,+4,+6,+10,+14,+17,+18,der(19)t(1;19)(q23;p13),+21,+21	n.d.
45	4/M	Karyotypic failure	FISH+, RT-PCR+
46	3/F	Karyotypic failure	RT-PCR+
47	1/M	Karyotypic failure	RT-PCR+

FISH, fluorescence *in situ* hybridization; n.d., not done; RT-PCR, reverse transcription–polymerase chain reaction; +, positive; −, negative.
*The karyotypes of cases 19 and 41 have previously been reported by Paulsson *et al* (2007).

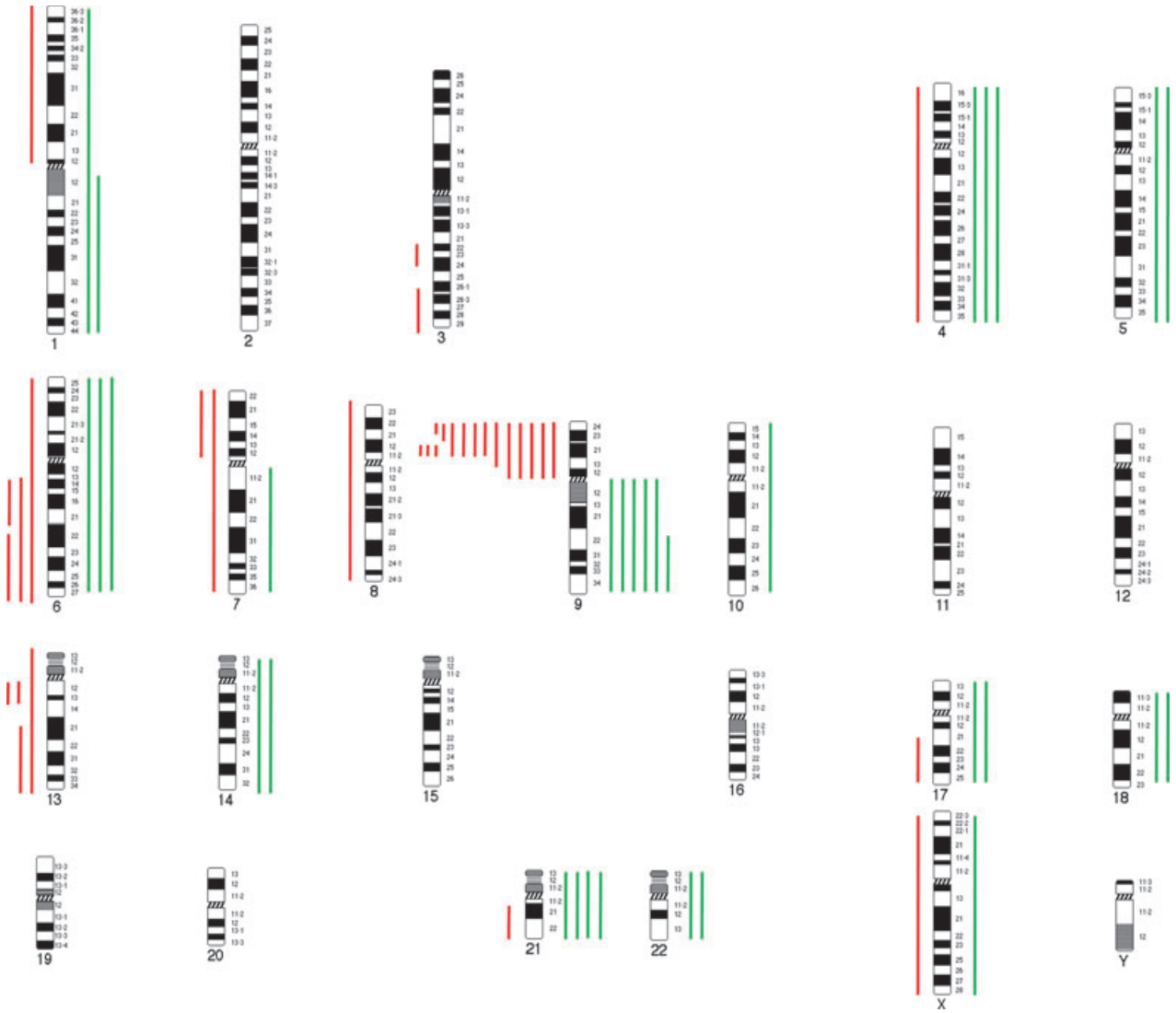

Fig 1. Map of additional genomic imbalances in t(1;19)/der(19)t(1;19) positive BCP ALL. Gains (green) are indicated to the right and losses (red) to the left of each chromosome.

that the inclusion of these patients was justified. The observed frequency of t(1;19)/der(19)t(1;19)-positive cases in the present series (1·8%) is lower than the 3–5% usually reported (Raimondi *et al*, 1990; Hunger, 1996; Uckun *et al*, 1998; Forestier *et al*, 2008a; Moorman *et al*, 2010). The reasons for this are probably manifold, including quite low numbers of patients in most series and decreased frequencies when only G-banding is performed. The latter explanation may well explain the overall low frequency in the present study considering that it increased from 1·0% in the 1992 NOPHO protocol to 3·0% in the 2000 protocol, in which FISH and/or RT-PCR analyses for *TCF3* rearrangement/*TCF3-PBX1* fusion were made mandatory. Furthermore, ethnic differences may also play a role, as previously suggested by Raimondi *et al* (1990).

The predicted EFS at 5 and 10 years in our study was 0·79, with one early death in remission and nine relapses occurring at a median of 23 months after diagnosis. This outcome is comparable to that of other recently reported studies (Table - IV). The 5-year OS of 0·85 in our series is also in good agreement with previous studies (Jeha *et al*, 2009; Moorman *et al*, 2010). When comparing t(1;19)-positive cases with cases of high hyperdiploidy and t(12;21)(p13;q22), EFS is not different between these groups in the Nordic countries but OS is worse. A similar difference in OS was also recently reported by Moorman *et al* (2010). This may indicate that relapses in patients with t(1;19) are more resistant to treatment than in patients in the 'standard risk group'. As a gradual increase in treatment intensity of childhood BCP ALL has occurred over the last three decades (Escherich *et al*, 2010; Mitchell *et al*, 2010; Pui *et al*, 2010; Salzer *et al*, 2010; Schmiegelow *et al*, 2010) one can speculate that this in itself could explain the improved prognosis reported for t(1;19) cases and thereby

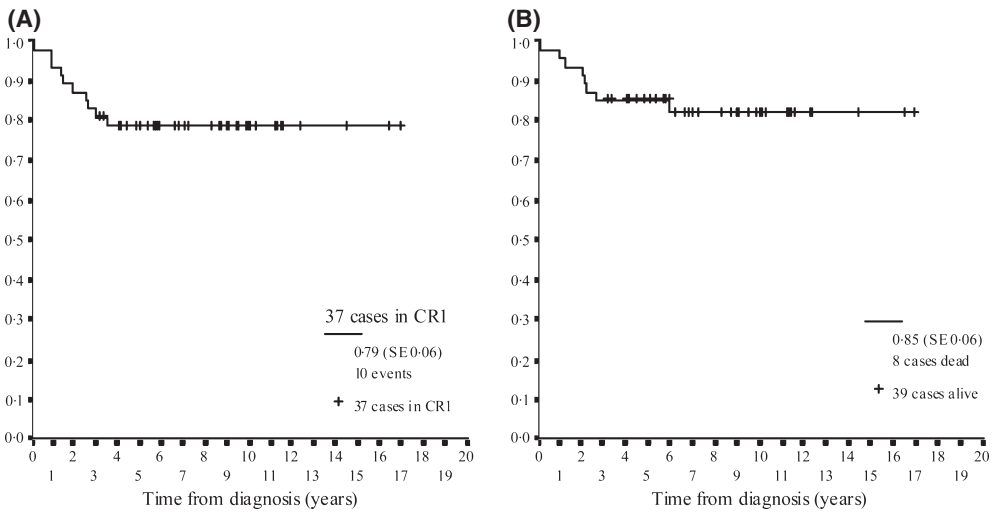

Fig 2. (A) Predicted EFS (pEFS) for 47 Nordic Children with t(1;19)(q23;p13) positive BCP ALL. (B) Predicted OS (pOS) for 47 Nordic Children with t(1;19)(q23;p13) positive BCP ALL. CR1, first complete remission.

Table II. Event-free and overall survival of patients with t(1;19)/der(19)t(1;19), t(12;21) and high hyperdiploidy among 2640 pre-B ALL cases treated on two successive NOPHO-protocols.

Genetics (N)	5-year EFS (SE)	10-year EFS (SE)	5-year OS (SE)	10-year OS (SE)
t(1;19 (47)	0·79 (0·06)	0·79 (0·06)	0·85 (0·05)	0·82 (0·06)
t(12;21) (399)	0·83 (0·02)	0·79 (0·02)	0·96 (0·01)	0·92 (0·02)
HeH (749)	0·81 (0·01)	0·79 (0·02)	0·91 (0·01)	0·89 (0·01)
P value	0·4		0·004	

Heh, high hyperdiploidy; EFS, event-free survival; OS, overall survival; SE, standard error of the mean.

have made stratification on the basis of t(1;19) obsolete. However, t(1;19)-positive cases were, in a recent study, reported to have a significantly higher incidence of CNS relapse than ALL patients without the translocation (Jeha *et al*, 2009; Table IV); the St Jude's group observed four patients with CNS relapse but no patients with bone marrow relapse among 41 patients with t(1;19) (Pui *et al*, 2010). Moorman *et al* (2010) reported six relapses in 50 patients with t(1;19) of which three relapses involved the CNS, but the numbers were too small to conclude that t(1;19) was associated with an increased risk of CNS relapse. In the present study we found no association with CNS relapse. The difference in relapse site may be due to the varying local treatment protocols. The CNS-directed therapy administered to children without CNS leukaemia at diagnosis in the two NOPHO protocols mainly consisted of ageadjusted intrathecal methotrexate, high dose methotrexate (5–8 g/m^2) and also, for high risk patients, high dose cytarabine. No CNS radiation was given as prophylaxis. It is not universally accepted what is actually CNS protective in the contemporary multi-drug therapy of ALL as the protection against the CNS leukaemia is probably not only due to the intrathecal therapy, but to the whole protocol as such. For this reason it is difficult to identify one component in the NOPHO protocol that can explain that no CNS relapses have occurred.

Table III. EFS and OS of various characteristics of patients with BCP ALL and t(1;19) or der(19)t(1;19) in the Nordic countries.

Group	No	5-year EFS (SE)	5-year OS (SE)	10-year EFS (SE)	10-year OS (SE)
t(1;19)	15	0·66 (0·12)	0·80 (0·10)	0·66 (0·12)	0·80 (0·10)
der(19)t(1;19)	29	0·83 (0·07)	0·86 (0·06)	0·83 (0·07)	0·81 (0·08)
Plain t(1;19)	17	0·82 (0·09)	0·82 (0·09)	0·82 (0·09)	0·82 (0·09)
t(1;19)+aberr	27	0·74 (0·08)	0·85 (0·07)	0·74 (0·08)	0·79 (0·09)
Male	21	0·86 (0·08)	0·90 (0·06)	0·86 (0·08)	0·84 (0·09)
Female	26	0·73 (0·09)	0·81 (0·08)	0·73 (0·09)	0·81 (0·08)
Age < 10 years	28	0·82 (0·07)	0·89 (0·06)	0·82 (0·07)	0·85 (0·07)
Age ≥ 10 years	19	0·73 (0·10)	0·79 (0·09)	0·73 (0·10)	0·79 (0·09)
WBC < 50 × 10^9/l	40	0·77 (0·07)	0·83 (0·06)	0·77 (0·07)	0·83 (0·06)
WBC ≥ 50 × 10^9/l	7	0·86 (0·13)	1·00 (0)	0·86 (0·13)	0·75 (0·22)

EFS, event-free survival; OS, overall survival; SE, standard error of the mean; WBC, white blood cell count.

Table IV. Recent studies on outcome of paediatric BCP-ALL with t(1;19)(q23;p13·3)/der(19)t(1;19)(q23;p13).

Study	No. of patients	5-year EFS	CNS relapse (no. of patients)
Baruchel *et al* (2005)	110	0·86	4
Kager *et al*, (2007)	31	0·90	1
Jeha *et al* (2009)	41	0·84	4
Moorman *et al* (2010)	50	0·80	3
Present study	47	0·79	0

Taken together, however, the outcome data support that patients with BCP-ALL and t(1;19) enrolled in the NOPHO protocol require more intensive therapy than low-risk/standard risk therapy alone.

Early studies of patients with t(1;19) reported an unexplained, poorer outcome of patients with the balanced t(1;19) compared with patients with the unbalanced form (Secker-Walker *et al*, 1992; Uckun *et al*, 1998). However, more recent studies – including the present one – found no difference in EFS among these two subgroups (Sharma *et al*, 2001; Kager *et al* 2007, Jeha *et al*, 2009). Thus, it seems safe to conclude that cases with t(1;19) or der(19) should not be stratified or treated differently.

Additional cytogenetic abnormalities were observed in 63% of the cases in this study, with no significant differences between t(1;19)- and der(19)-positive cases. The most common secondary structural abnormalities were del(9p), i(9q), del(6q) and del(13q); this is in good agreement with the data reported by Secker-Walker *et al* (1992). In particular, loss of 9p as a result of a deletion of 9p, an unbalanced translocation, or the formation of an isochromosome 9q was the most frequent abnormality. Chromosome arm 9p harbours the tumour suppressor gene *CDKN2A*, which is often inactivated in haematological malignancies (Krug *et al*, 2002). In fact, deletion of this gene is particularly frequent in childhood ALL with t(1;19). Sulong *et al* (2009) found deletions of *CDKN2A* in 42% of patients with t(1;19). Loss of 9p material was observed in 34% of cases in our study; however, it should be emphasized that FISH or other methods were not consistently performed to identify submicroscopic deletions. Another target gene of the 9p deletions may be the *PAX5* gene, which plays an important role in B-cell commitment and maintenance (Nutt *et al*, 1999) and which by single nucleotide polymorphism arrays has been shown to be recurrently deleted in various cytogenetic subtypes of childhood ALL, including t(1;19) positive cases (Mulligan *et al*, 2007; Kawamata *et al*, 2008; Paulsson *et al*, 2010). Mulligan *et al* (2007) also detected various submicroscopic deletions of 13q in eight out of 17 patients with t(1;19) of which the *RB1* gene was the target of deletion in two patients.

The presence of additional cytogenetic abnormalities had no impact on EFS or OS in the present cohort. This observation is in line with findings from other recurrent leukaemia-associated translocations, where additional cytogenetic abnormalities seem to have no influence on prognosis (Grimwade *et al*, 1998; De Botton *et al*, 2000). Apart from cases with del(9p) the number of patients with identical additional abnormalities in this study is too small to rule out subgroups of prognostic significance. As regards the prognostic impact of del(9p), this was not addressed in the present study because the true incidence of del(9p) in the cohort is unknown (only a few cases were analysed by FISH for 9p deletions). Two of the 47 cases had a modal number above 50. In addition to the t(1;19), these cases (Cases 43 and 44; Table I) had a high hyperdiploid karyotype characteristic of BCP ALL, i.e., gains of chromosomes X, 4, 6, 10, 14, 17, 18, and 21 (Paulsson & Johansson, 2009). This underscores that one should look specifically for t(1;19) also in 'high hyperdiploid' cases as the identification of t(1;19) may lead to a change in risk group assignment.

In conclusion, t(1;19)(p23;q13) is a 'non-standard risk' translocation seen in 1·0–3·0% of all childhood BCP ALLs diagnosed in the Nordic countries. It is not associated with increased risk of CNS relapse, and EFS and OS are not influenced by the presence of additional cytogenetic aberrations or whether the translocation is balanced or unbalanced.

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Author contributions

M.K.A., E.F., and B.J. designed the study. M.K.A. and E.F. analysed the data. All authors participated in reviewing the karyotypes and writing the paper.

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