Incidence and outcome of *TCF3-PBX1*-positive acute lymphoblastic leukemia in Austrian children

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ABSTRACT

Lessons from the analysis of children with *TCF3-PBX1* ALL could help to identify treatment components essential for this leukemia subtype. Of 859 children with ALL who were treated in ALL-BFM trials in Austria, 31 (3.6%) had a *TCF3-PBX1* ALL. The 5-year event-free survival rate for these 31 patients was 90%±5%. Patients with *TCF3-PBX1* ALL treated on the ALL-BFM 86 trial had a poorer outcome than patients with *TCF3-PBX1* ALL treated on later trials. These data document that contemporary ALL-BFM treatment is highly effective in children with *TCF3-PBX1* ALL. Implementation of early dose-intensified remission induction may be an essential treatment component.

Key words: outcome, *TCF3-PBX1*, acute lymphoblastic leukemia.

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The translocation t(1;19)(q23;p13) occurs in about 5% of children with acute lymphoblastic leukemia (ALL).[1] It is identified more often in Africans;[2] however, the exact incidence in Caucasians is unknown. In 90-95% it results in a fusion of TCF3 (E2A) at 19p13 with PBX1 at 1q23 thereby creating a *TCF3-PBX1* fusion gene that encodes a protein with transforming properties.[1] Cytogenetically, it is identified as unbalanced der(19)t(1;19) or as balanced t(1;19) with some patients displaying both balanced and unbalanced translocations.[3] This ALL subtype is associated with the pre-B immunophenotype.[1] When treated on conventional antimetabolite based therapy protocols, children with t(1;19)/*TCF3-PBX1* ALL had poor outcomes,[4-7] but the more recently introduced treatment intensification protocols improved prognosis.[8-10] However, it is unknown which treatment element(s) are responsible for this therapeutic success. To address this issue and to estimate the incidence of *TCF3-PBX1* ALL in Caucasian children, we have analyzed the data of 859 Austrian children with ALL who were treated on four consecutive Berlin-Frankfurt-Muenster (BFM) ALL trials.

Design and Methods

From October 1986 to October 2003, 859 Caucasian children (≤18 years of age) with newly diagnosed ALL were enrolled in the trials of the BFM group in Austria; ALL-BFM 86 (n=142), ALL-BFM 90 (n=256), ALL-BFM 95 (n=230), and ALL-BFM 2000 (n=231), contingent on informed written consent. All studies were approved by the local ethics committee. ALL was diagnosed and centrally reviewed according to standard criteria.[11] The diagnosis of t(1;19)/*TCF3-PBX1* was centrally established based on banded metaphase karyotyping, fluorescence in situ hybridization (FISH), and/or reverse-transcriptase polymerase chain reaction (RT-PCR) on diagnostic leukemia cells using standard methods.[12-14] The definition and description of clonal abnormalities followed the recommendations of ISCN (2005). Since 1991, all diagnostic BM and/or PB samples were prospectively screened for *TCF3-PBX1* transcripts via RT-PCR; samples from all patients diagnosed prior to 1991 were obtained from the reference cytogenetic laboratory and analyzed retrospectively. In all patients with a diagnosis of *TCF3-PBX1* ALL additional RT-PCR analyses

were performed on BM and/or PB follow-up samples. *TCF3-PBX1* transcripts were measured via quantitative real-time RT-PCR since 1999. FISH analysis – using the TCF3 dual color split signal probe (Dako Cytomation, Denmark) according to the manufacturer's recommendation – was performed retrospectively in all patients in whom RT-PCR revealed *TCF3-PBX1* ALL and from whom material was available. Details on treatment stratification and protocols used in the four treatment trials have been published elsewhere.[11,15] Response to treatment was assessed as previously described.[11]

Survival was calculated using the Kaplan-Meier method together with standard errors. Event-free survival was calculated from diagnosis until relapse or death from any cause, whichever occurred first. Differences between survival curves were evaluated using the log-rank test. All statistical analyses were performed in R version 2.4.0 software (*http://www.r-project.org/*).

Discussion and Results

In this investigation, the *TCF3-PBX1* fusion gene was identified in 31 (3.6%) of 859 children with ALL. Characteristics of leukemia cells of these 31 patients are provided in Table 2 (*online appendix*). Karyotyping was successful in 27 of the 31 patients, and a t(1;19) was detected in 17 patients. FISH analysis was performed retrospectively in 25 of 31 patients with a *TCF3-PBX1* ALL, and the t(1;19) was confirmed in all cases. In contrast to some previous reports which focused on conventional cytogenetics only,[6,7] our FISH analyses revealed no difference in the frequency between balanced only (n=10) and unbalanced only translocations (n=10). In five cases both balanced and unbalanced variants were present, albeit in two distinct clones (*Table 1, online appendix*).

This observation is in line with the model put forward by Paulsson et al. that an unbalanced der(19) most likely arises from an initial trisomy 1 followed by a t(1;19) and the subsequent loss of the der(1).[16] A relationship between two such clones can be further deduced from the fact that in case 14 they also share a secondary abnormality in form of an i(7q). The replacement of the normal chromosome 19 with a duplicated der(19) in case 17, on the other hand, represents a rather unique evolutionary pathway, which also concurred with an extraordinary FISH signal pattern. Apart from the expected corresponding pattern 2R-1G-0F, we also found a 3R-1G-1F configuration in a significant proportion of nuclei. This fusion signal consisted of a large green 3' and a tiny red 5' *TCF3* signal that for technical reasons was probably not always visible. As evidenced on metaphase spreads this fusions was situated on the der(1), which implies that in this particular case the break in the *TCF3* gene had probably occurred somewhere between exons 1 and 7 rather than in the otherwise common 3,5kb breakpoint cluster region between exons 15 and 16, but nevertheless resulted in the typical RT-PCR detectable

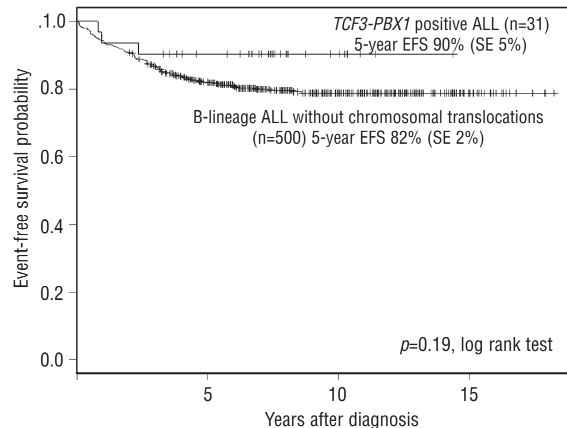

Figure 1. Kaplan-Meier curves of event-free survival for 31 patients with *TCF3-PBX1* positive ALL and a control group of 500 patients with B-lineage ALL (excluding *TEL-AML1*, BCR-ABL, and MLL rearranged cases). The 531 patients were treated on four consecutive ALL-BFM trials in Austria between October 1986 and October 2003. Tick marks indicate individual patients who have not yet reached the critical event. *Details, see text.*

fusion transcript.

In line with published data,[1] the pre-B immunophenotype was found in 70%, and a common ALL phenotype in 30% of our patients with *TCF3-PBX1* ALL s (*Table 1, online appendix*). Presenting features and pertinent clinical data of the 31 children (male, n=17; female, n=14) with TCF3-PBX1 ALL are provided in Table 1. Median age at diagnosis was 6.9 years (range, 1.2 to 17 years); and median diagnostic WBC was 20.7×10^9/L (range, 3.9 to 148.5×10^9/L). Twenty of the 31 patients were stratified into the medium risk, nine into the standard risk, and only two into the high risk treatment arms. *Response to prednisone* was good in 29 patients and 19 of 26 analyzed patients had M1 bone marrow on day 15. The treatment induced remission in all 31 patients on day 33 of therapy.

The 5-year event free survival (EFS) rate of the 31 children with *TCF3-PBX1* ALL was 90± 5% (95% confidence interval (CI) 81% to 100%) (Figure 1). Median follow-up of the 28 survivors was 7.5 years (range, 3.3 to 14.4 years). Three children relapsed very early (10 and 11 months after diagnosis) or early (28 months after diagnosis), and all three subsequently died from disease. Our result is in line with a recent report from the French FRALLE Study Group, in which all 17 relapses in 110 children with t(1;19)/*TCF3-PBX1* ALL occurred within 30 months from diagnosis.[17]

In our cohort of children with *TCF3-PBX1* ALL outcome differed among protocols, and prognosis was better for the 26 patients treated on ALL-BFM 90 (n=7; 5-year EFS 86±13%), ALL-BFM 95 (n=10; 5-year EFS 100%), and ALL-BFM 2000 (n=9; 5-year EFS 100%) protocols compared to the five patients treated on the ALL-BFM 86 protocol (ALL-BFM 86; n=5, 5-year EFS 60±22%, 95% CI 30% to 100% versus other protocols; n=26, 5-year EFS 96±4%, 95% CI 89% to 100%; p=0.014). Conversely, no difference in outcome was observed between these proto-

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Table 1. Patient characteristics, treatment, course, and outcome of 31 children with *TCF3-PBX1* positive ALL.

No.	Sex/age (years)	WBC ($\times 10^9$/L)	CNS*	Therapy**	PDR†	BM evaluation on days 15/33§	*TCF3-PBX1* transcripts at diagnosis (D) and during course (months) Bone Marrow	Peripheral Blood	Relapse (months) Treatment	Outcome (years)
1	M/10.5	3.9	CNS1	86-SR	Good	NT/M1	Pos (D), pos (28)	Neg (18), pos (24)	BM (28), CHT, no CR, MSD-SCT	DOD (3)
2	F/7.9	10.5	CNS1	86-MR	Good	NT/M1	Pos (D), pos (24)	Neg (24)	–	CCR (14.4)
3	M/13.8	148.5	CNS1	86-MR	Good	NT/M1	Pos (D), neg (36)	Neg (36)	–	CCR (9.7)
4	F/3.6	85.8	CNS1	86-HR	Poor	NT/M1	Pos (D), pos (6, 11)	NT	BM+CNS (11), CHT, CR 2 (12), BM (13)	DOD (1.2)
5	F/4.1	21.8	CNS1	86-HR	Poor	NT/M1	Pos (D), pos (29), neg (42, 47)	Pos (27)	–	CCR (6.2)
6	F/10	99.6	CNS3	90-MR	Good	M1/M1	Pos (D), neg (5), neg (26)	Neg (10)	–	CCR (10.4)
7	F/12.7	12.6	CNS1	90-MR	Good	M2/M1	Pos (D), pos (10)	NT	BM (10), CHT + Interferon-α PD	DOD (1.1)
8	M/2.2	8.9	CNS1	90-MR	Good	M1/M1	Pos (D), neg (25), pos (37), neg (38)	NT	–	CCR (11.4)
9	M/14.9	7.8	CNS1	90-SR	Good	M1/M1	Pos (D), neg (25)	NT	–	CCR (10)
10	F/2.0	34.0	CNS1	90-MR	Good	M1/M1	Pos (D), neg (37)	NT	–	CCR (10.8)
11	M/17	13.5	CNS1	90-MR	Good	M1/M1	Pos (D), neg (3, 5, 8, 11, 30)	NT	–	CCR (7.4)
12	M/11.6	76.4	CNS1	90-MR	Good	M2/M1	Pos (D), neg (6, 26)	neg (6)	–	CCR (10.2)
13	F/12	18.6	CNS1	95-MR	Good	M2/M1	Pos (D), pos (0.5), pos (3), neg (8, 24)	NT	–	CCR (7.8)
14	F/13.9	16.0	TLP+	95-MR	Good	M1/M1	Pos (D), neg (0.5, 3, 5, 13, 26)	NT	–	CCR (7.1)
15	F/6.9	6.1	TLP-	95-MR	Good	M1/M1	Neg (1, 4, 6, 12, 24)	Pos (D), neg (0.5)	–	CCR (6.7)
16	F/3.7	10.4	CNS1	95-SR	Good	M1/M1	Pos (D), pos (0.5), neg (3, 5, 7, 12, 24)	NT	–	CCR (8)
17	M/4	19.8	CNS2	95-SR	Good	M1/M1	Pos (D), neg (1, 6, 37)	NT	–	CCR (7.5)
18	M/2.2	24.1	CNS1	95-MR	Good	M2/M1	Pos (D), neg (0.5, 1, 5)	NT	–	CCR (7.5)
19	M/8.6	7.2	CNS1	95-MR	Good	M1/M1	Pos (D), neg (5)	NT	–	CCR (8.7)
20	M/2.9	42.5	TLP+	95-MR	Good	M1/M1	Pos (D), neg (0.5, 3, 25)	NT	–	CCR (8)
21	F/2.3	130.9	CNS1	95-MR	Good	M1/M1	Pos (D), neg (3, 12, 25)	Neg (0.5)	–	CCR (6.6)
22	F/13.9	28.5	CNS1	95-SR	Good	M1/M1	Pos (D), pos (24), neg (36)	NT	–	CCR (10.3)
23	F/3.6	64.9	CNS1	2000-SR	Good	M2/M1	Pos (D), neg (1, 2, 3, 6, 12)	Neg (0.5, 2)	–	CCR (3.5)
24	M/3.5	11.8	CNS1	2000-MR	Good	M2/M1	Pos (D), pos (1, 2), neg (12)	Pos (D), Pos (0.5), neg (2, 3)	–	CCR (3.3)
25	M/15.1	20.7	CNS1	2000-MR	Good	M1/M1	Pos (D), neg (1, 2, 3, 5, 7, 24)	NT	–	CCR (7.3)
26	M/1.8	96.2	CNS2	2000-SR	Good	M1/M1	Pos (D), neg (5, 12, 24)	Pos (D), neg (0.5, 3), pos (1)	–	CCR (5.7)
27	M/1.2	58.6	CNS1	2000-MR	Good	M1/M1	Pos (D), neg (0.5, 1, 2, 5, 13, 18, 24, 37)	Neg (24)	–	CCR (7.6)
28	F/2.4	39.8	CNS1	2000-SR	Good	M2/M1	Pos (D), neg (1, 2, 3, 5)	NT	–	CCR (7)
29	M/14.9	9.8	CNS1	2000-MR	Good	M1/M1	Pos (D), pos (0.5), neg (1, 3, 5, 6, 10)	Pos (D), neg (0.5, 1)	–	CCR (4.6)
30	M/1.7	14.3	CNS1	2000-MR	Good	M1/M1	Pos (D), neg (3, 5, 12, 20, 25)	Pos (D)	–	CCR (3.8)
31	M/9.9	25.4	CNS1	2000-SR	Good	M1/M1	Pos (D), neg (1, 2, 3, 5)	Pos (D), pos (0.3), neg (0.5)	–	CCR (4)

*Time points of minimal residual disease evaluation, relapse, and follow up recorded as time since diagnosis of ALL. BM: bone marrow; CHT: chemotherapy; CR: complete remission; CCR: complete continuous remission; D: diagnosis; DOD: died of disease; MSD-SCT: matched sibling donor stem cell transplantation; NT: not tested; PD: progressive disease. *CNS,: central nervous system: CNS1: no blasts in the cerebrospinal fluid cytospin; CNS2: blasts present, but leukocytes less than 5/μL; CNS3: blasts present and leukocytes more than 5/μL, patients with a traumatic lumbar puncture (TLP; >10 erythrocytes/mL) were classified as TLP+ (blasts present) or TLP– (no blasts). **Treatment according to the BFM protocol active at the time of enrolment (SR: standard risk; MR: medium risk; HR: high risk). †PDR: prednisone response (good response <1x10⁹/L lymphoblasts in PB after 7 days prednisone therapy and one initial i.th. dose of methotrexate). §Bone marrow evaluations (BM) during remission induction therapy (Days 15 and 33 of treatment); M1 <5% leukemic blast cells; M2 ≥5% to 25% leukemic blast cells.*

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cols in patients with B-lineage ALL (excluding TEL-AML1, BCR-ABL, and MLL rearranged cases) (ALL-BFM 86; n=82, 5-year EFS 78±5% versus ALL-BFM 90, 95, 2000; n=418, 5-year EFS 83±2%; p=0.67).

Although cumulative anthracycline dose was higher during induction therapy in the ALL-BFM 86 trial, higher dose intensity (by combining more drugs in a shorter period of time) was administered during induction in the trials ALL-BFM 90, 95, and 2000.[11] Clearly, our data need to be interpreted with caution, as the number of patients with *TCF3-PBX1* ALL is low. However, our results suggest that early intensive remission induction therapy may be an essential treatment element in patients with this ALL subtype. Interestingly, prognosis was better for 75 children with t(1;19)/*TCF3-PBX1* ALL who were treated on Pediatric Oncology Group protocol 9005/6 (prednisone (P), vincristine (V), L-asparaginase (Asp) or PVAsp + doxorubicin induction; 5-year EFS 75%) when compared to 67 children treated on POG 8602 protocol (PVAsp induction, 5-year EFS 58%).[18] A similar trend was observed in United Kingdom Medical Research Council protocol for ALL studies, namely UKALLX (PVAsp + daunorubicin induction, 5-year EFS 88%) and UKALLXI (PVAsp induction since 1992, 5-year EFS 72%).[19] Clearly, further investigations are necessary to define the importance of early dose intensive remission induction therapy in this ALL subtype in a large series of patients.

Minimal residual disease (MRD) diagnosis based on *TCF3-PBX1* fusion transcripts was performed in 14 patients after completion of induction therapy (negative,

n=13; positive n=1), and in 17 patients after completion of induction consolidation therapy (negative, n=17), all of whom remained in CR a median of seven years (range, 3 to 10.4 years) from diagnosis (Table 1). There was a trend towards better outcomes in patients in whom all follow-up PCR results for *TCF3-PBX1* fusion transcripts were negative (n=18, 5-year EFS 100%), compared to patients who had at least one positive PCR result during follow-up before diagnosis of relapse (n=12, 5-year EFS 83±11%) (p=0.08). Interestingly, four of five patients treated according to the ALL-BFM 86 protocol had positive PCR MRD results during follow-up, and two of these patients relapsed; whereas non of the eight patients with positive PCR MRD results during follow-up, who received treatment according to the ALL-BFM-90, -95, and -2000 protocols, relapsed (Table 1). Although our data must be interpreted with caution due to the low number of patients studied, the results of our recent protocols are in line with earlier studies, which also failed to detect a significant difference in outcome based on MRD analyses.[14,20] In contrast to some previous reports,[6,7,9] we found no difference in outcome between children who had clones with balanced t(1;19) (n=10, 5-year EFS 100%), unbalanced t(1;19) (n=10, 5-year EFS 90±9%), or a combination of balanced and unbalanced t(1;19) (n=5, 5-year EFS 80±18%)(p=0.38).

Despite some limitations (e.g., low number of patients, four different trials with differences in treatment intensity and -stratification), our data provide evidence, that treatment according to contemporary BFM and similar protocols holds the promise to achieve excellent outcomes in Caucasian children with *TCF3-PBX1* ALL, which may be in part attributable to the implementation of early dose-intensified remission induction. No patient stratification seems to be necessary based on *TCF3-PBX1* status in current BFM protocols.

Authors' Contributions

LK analyzed the data and wrote the paper, TL, SS, OAH, MND performed research and analyzed the data, AA analyzed the data, MK performed research, MS, HG, and GM designed research.

Conflict of Interest

The author reported no potential conflicts of interest.

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