LETTER OPEN

ACUTE LYMPHOBLASTIC LEUKEMIA

PAX5::*AUTS2* childhood B-ALL: a relapse-prone genetic subtype with frequent central nervous system involvement and a poor outcome

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TO THE EDITOR:

In childhood and young adolescent B-cell precursor acute lymphoblastic leukemia (B-ALL) *PAX5* is one of the most frequent targets of genetic alterations comprising deletions, intragenic amplifications (*PAX5*^{AMP}), and point mutations as well as rearrangements (*PAX5*-r) with multiple partner genes [1]. *PAX5*-r account for 2–3% of all newly diagnosed B-ALL cases and result in the expression of fusion oncoproteins [1, 2].

Patients with *PAX5*-r tend to have higher relapse and poorer overall survival (OS) rates compared to good-risk genetic groups [3–5]. Recent studies indicate that *PAX5*-r is associated with the *IKZF1*^{plus} copy number alteration (CNA) profile and a rather poor event-free survival (EFS) [3, 5]. In small cohorts of infant B-ALL, *PAX5*-r patients had a worse outcome than those with other non-*KMT2A* genetic subtypes [6, 7].

Most, but not all, cases with *PAX5*-r belong to the *PAX5*-altered (*PAX5*alt) subtype identified by gene expression profiling [1]. *PAX5*alt is associated with an intermediate to poor prognosis with a strong dependence on *IKZF1* codeletion [1, 8, 9]. Despite sharing a distinctive expression signature, the underlying genetic landscape of *PAX5*alt is heterogeneous and various types of *PAX5* lesions, which differently affect disease biology and outcomes, are merged into a single group [1, 9]. Moreover, *PAX5* is fused to a multitude of different partner genes, and since most of these fusions have been detected only in a few cases [1], the impact of individual *PAX5*-r on outcomes remains to be determined.

In this international study, we collected cases with *PAX5*::*AUTS2* B-ALL diagnosed over the past decades in patients aged 0–18 years, without any time or study protocol restrictions, to evaluate the prognostic relevance of this rare genetic subtype. In accordance with the Declaration of Helsinki, patients were enrolled in respective clinical trials with written informed consent from their parents or legal guardians, and the use of surplus diagnostic material for research purposes was approved by the institutional review boards of the participating centers.

Patients with a confirmed *PAX5*::*AUTS2* fusion detected by RT-PCR or a next-generation sequencing (NGS) approach were eligible for inclusion in the study. Additionally, since *PAX5*::*AUTS2* frequently results from unbalanced der(9)t(7;9)(q11;p13) rearrangements, cases with breakpoints in both *PAX5* and *AUTS2* detected by single nucleotide polymorphism (SNP) array analysis were included without additional molecular genetic verification,

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Table 1. Demographic, clinical, genetic characteristics and outcome of *PAX5*::*AUTS2* patients.

Age group	Children (>1 year) $n = 42$	Age <18 months $n = 18$	Infants (≤1 year) $n = 8$	All patients $n = 50$
Gender				
Female	42.9% (18/42)	38.9% (7/18)	25.0% (2/8)	40.0% (20/50)
Male	57.1% (24/42)	61.1% (11/18)	75.0% (6/8)	60.0% (30/50)
Age				
Median age in years (range)	2.3 (1.1–15.5)	1.1 (0.6–1.4)	0.9 (0.6–1.0)	2.0 (0.6–15.5)
≤1 year	–	–	–	16.0% (8/50)
>1–3 years	78.6% (33/42)	–	–	66.0% (33/50)
>4–9 years	16.7% (7/42)	–	–	14.0% (7/50)
≥10 years	4.8% (2/42)	–	–	4.0% (2/50)
WBC 10^9/L				
Median (range)	40.1 (1.2–537.6)	57.0 (2.7–315.0)	53.0 (3.9–299.7)	40.1 (1.2–537.6)
<20	35.7% (15/42)	27.8% (5/18)	25.0% (2/8)	34.0% (17/50)
≥20	16.7% (7/42)	22.2% (4/18)	25.0% (2/8)	18.0% (9/50)
≥50	47.6% (20/42)	50.0% (9/18)	50.0% (4/8)	48% (24/50)
CNS involvement				
Yes[a]	21.4% (9/42)	33.3% (6/18)	62.5% (5/8)	28.0% (14/50)
No	78.6% (33/42)	66.7% (12/18)	37.5% (3/8)	72.0% (36/50)
IKZF1^{plus}				
Yes	66.7% (26/39)	60.0% (9/15)	33.3% (2/6)	62.2% (28/45)
No	33.3% (13/39)	40.0% (6/15)	66.7% (4/6)	37.8% (17/45)
Unknown	7.1% (3/42)	16.7% (3/18)	25.0% (2/8)	10.0% (5/50)
Prednisone response				
Good	78.8% (26/33)	56.3% (9/16)	62.5% (5/8)	75.6% (31/41)
Poor	21.2% (7/33)	43.8% (7/16)	37.5% (3/8)	24.4% (10/41)
Unknown	21.4% (9/42)	16.7% (2/18)	0.0% (0/8)	18.0% (9/50)
MRD				
FCM day 15 ≥10%	26.3% (5/19)	40.0% (4/10)	50.0% (2/4)	30.4% (7/23)
PCR and/or FCM EOI positive[b]	82.1% (32/39)	64.3% (9/14)	60.0% (3/5)	79.5% (35/44)
MRD EIO $\geq 5 \times 10^{-4}$	40.6% (13/32)	44.4% (4/9)	20.0% (1/5)	31.8% (14/44)
MRD EOI $< 5 \times 10^{-4}$	65.4% (19/32)	55.6% (5/9)	40.0% (2/5)	47.7% (21/44)
MRD EOI negative	17.9% (7/39)	35.7% (5/14)	20.0% (2/5)	20.5% (9/44)
PCR and/or FCM EOC positive[c]	32.4% (11/34)	25.0% (3/12)	0.0% (0/3)	29.7% (11/37)
Relapse				
Yes	42.9% (18/42)	61.1% (11/18)	62.5% (5/8)	46.0% (23/50)
BM[d]	72.2% (13/18)	63.6% (7/11)	40.0% (2/5)	65.2% (15/23)
CNS	11.1% (2/18)	18.2% (2/11)	20.0% (1/5)	13.0% (3/23)
BM & CNS	16.7% (3/18)	18.2% (2/11)	40.0% (2/5)	21.7% (5/23)
No	57.1% (24/42)	38.9% (7/18)	37.5% (3/8)	54.0% (27/50)
Outcome				
Dead	19.0% (8/42)	27.8% (5/18)	25.0% (2/8)	20.0% (10/50)
Leukemia	37.5% (3/8)	20.0% (1/5)	0.0% (0/2)	30.0% (3/10)
Treatment-related complications	37.5% (3/8)	40.0% (2/5)	50.0% (1/2)	40.0% (4/10)
Other cause/unknown	25.0% (2/8)	40.0% (2/5)	50.0% (1/2)	30.0% (3/10)
Alive	81.0% (34/42)	72.2% (13/18)	75.0% (6/8)	80.0% (40/50)

WBC white blood cell count, *CNS* central nervous system, *MRD* measurable residual disease, *FCM* flow cytometry, *EOI* end of induction, *EOC* end of consolidation, *BM* bone marrow.
[a]including patients with CNS2, CNS3, traumatic lumbar puncture with leukemia blasts or reported as positive without any further classification.
[b]days 28-42 of therapy.
[c]days 78-112 of therapy.
[d]one childhood patient had an extramedullary testis involvement.

likewise cases identified by optical genome mapping (OGM). All *PAX5*::*AUTS2* fusion transcripts were in frame or at least predicted to be. CNA profiling for *IKZF1* deletion and *IKZF1*^{plus} was performed by SNP array, multiplex ligation-dependent probe amplification (MLPA), digitalMLPA or OGM following standard procedures (Supplementary Methods).

The Kaplan–Meier method was used to determine EFS and OS rates and the analysis was performed in R (version 4.2.2) statistical environment. Adverse events were defined as relapse at any site, the development of a second malignant neoplasm (SMN), or death from any cause. OS was defined as the time from diagnosis to the date of last follow-up or death. The cumulative incidence of relapse (CIR) was calculated using the Kalbfleisch and Prentice method and compared with the Gray's test considering death and SMN as competing events. Multivariate analysis was conducted using a Cox proportional hazards regression model.

We identified 50 patients diagnosed with *PAX5*::*AUTS2* B-ALL, including 16 previously published cases (Supplementary Table S1). The main demographic and clinical features showed a male predominance (60% vs 40%), a median age of 2.0 years (range 0.6–15.5 years), including eight infants (≤1 year), and highly variable white blood cell counts (WBC) ranging from 1.2–537.6 × 10^9/L (median 40.1 × 10^9/L) (Table 1).

We detected *IKZF1* deletions in 69.6% (32/46 with available data) of *PAX5*::*AUTS2* cases, most displaying also *CDKN2A/B* (90.0%, 27/30) and/or *PAX5* (87.1%, 27/31) deletions (Supplementary Table S1). Based on this deletion pattern, 62.2% (28/45) showed the *IKZF1*^{plus} CNA profile [10] (Table 1), which is higher than reported for childhood *PAX5*alt (20–30% *IKZF1*-deleted, 20% *IKZF1*^{plus}) or *PAX5*^{AMP} (13% *IKZF1*^{plus}) cases [1, 9, 11].

According to National Cancer Institute (NCI) criteria (age ≥10 years and/or WBC ≥50 × 10^9/L; infants), 60.0% (30/50) of patients had high-risk (HR) status. Of the patients with available data, 24.4% (10/41) showed a poor prednisone response (Table 1), which is ~15% higher than in the average population of childhood B-ALL [10]. Measurable residual disease (MRD) data assessed by flow cytometry (FCM) on day 15 were only available for 23 patients, and according to AIEOP-BFM definitions, 30.4% (7/23) showed HR disease with ≥10% residual blast cells [12]. At the end of induction therapy (EOI; days 28-42), PCR- and/or FCM-MRD measurements showed that 79.5% (35/44) of patients were MRD-positive: 31.8% (14/44) ≥5×10^{-4} and 47.7% (21/44) <5 × 10^{-4}. At the end of consolidation therapy (EOC; mainly day 78; range 71–117 days), 29.7% (11/37) of patients still presented with MRD, but except for two (≥5 × 10^{-4}), with levels ≤1 × 10^{-4} (Table 1 and Supplementary Table S1).

Overall, 46.0% (23/50) of *PAX5*::*AUTS2* patients experienced a relapse with a median time-to-event of 1.6 years (range 0.6-4.1 years) with the majority (65.2%, 15/23) occurring within two years after diagnosis (Fig. 1A; Supplementary Table S1). Most patients

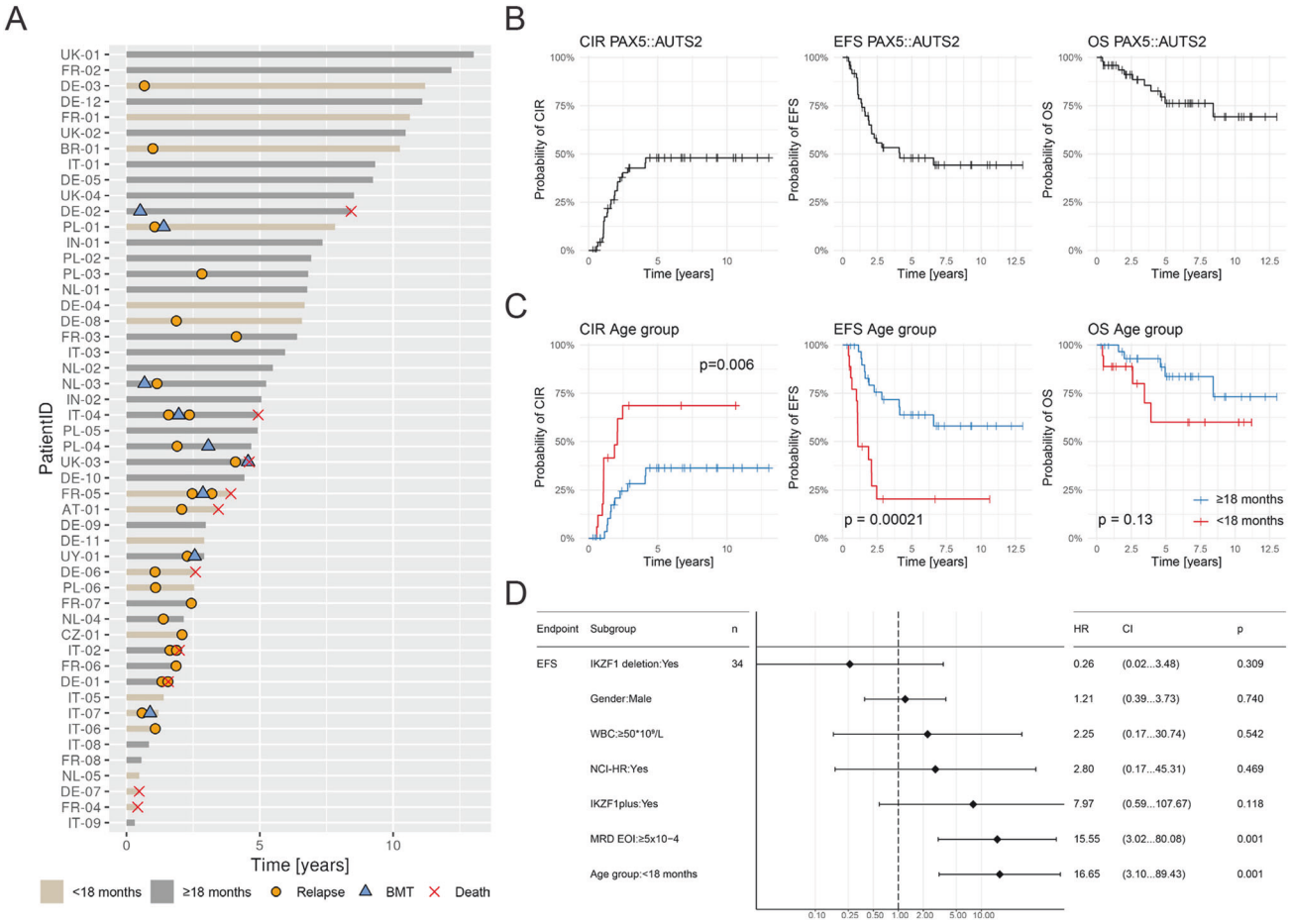

Fig. 1 Course of disease and outcome of *PAX5*::*AUTS2* patients. A Swimmer plot illustrating the clinical course of each individual patient. Relapses (orange dots), bone marrow transplantation (BMT; blue triangles), and death (red crosses) as well as age groups <18 months (light brown bars) and ≥18 months (gray bars) are indicated. **B**–**C** Cumulative incidence of relapse (CIR) and Kaplan-Meier survival curves of event-free (EFS) and overall survival (OS), (**B**) of all *PAX5*::*AUTS2* cases ($n = 50$), (**C**) based on age group; red, <18 months; blue, ≥18 months. Gray's test *p*-value for CIR, Log-ranks test *p*-values for EFS and OS. **D** Forrest plot showing results of multivariate Cox regression analysis. HR hazard ratio, CI confidence interval, *p* Gray's test *p*-value, WBC white blood cell count, NCI-HR National Cancer Institute high-risk, MRD-EOI (measurable residual disease) determined by PCR and/or flow cytometry at the end of induction (EOI) therapy.

had isolated bone marrow (BM; 60.9%, 14/23) relapses, but CNS disease was detected in 34.8% (8/23) of patients mostly combined with BM recurrence (Table 1). In total, 38.0% (19/50) of patients had CNS disease: 22.0% (11/50) only at diagnosis, 6.0% (3/50) at diagnosis and relapse, and 10.0% (5/50) only at relapse. Among infants, 87.5% (7/8) had CNS involvement, with 62.5% (5/8) already at diagnosis (Supplementary Methods), one patient at both time points, and two additional cases only at relapse (Supplementary Table S1). CNS disease was more frequently detected in infants than in children [87.5% (7/8) vs 40.0% (12/30), Fisher exact test $p = 0.0031$].

The 5-year CIR for all patients was 48.0 ± 7.8% (Fig. 1B) and of the patients who relapsed, 17.4% (4/23) experienced a second BM relapse within 3–9 months of the first (Fig. 1A). Among patients experiencing a relapse, 30.4% (7/23) died, three of progressive disease and four of treatment-related mortality (TRM), and in total, 20.0% (10/50) of patients died ($n = 3$ leukemia, $n = 4$ TRM, $n = 3$ other/unknown reasons) (Fig. 1A, Table 1 and Supplementary Table S1).

With a median follow-up of 4.8 years (range 0.3–13.0 years), we observed 5-year EFS and OS rates for all patients of 47.9 ± 7.6% and 76.2 ± 7.1%, respectively, (Fig. 1B). Notably MRD levels ($\geq 5 \times 10^{-4}$ vs $< 5 \times 10^{-4}$ vs negative) at EOI did not significantly impact CIR, EFS or OS (Supplementary Fig. S1A), suggesting that in *PAX5*::*AUTS2* patients EOI-MRD negativity does not predict a favorable outcome. Patients with $\geq 5 \times 10^{-4}$ EOI-MRD had a worse EFS compared to cases with $< 5 \times 10^{-4}$/negative EOI-MRD, but the result did not reach statistical significance ($p = 0.057$) (Supplementary Fig. S1B). Furthermore, we did not find any differences in 5-year EFS and OS between *IKZF1*^{plus} and non-*IKZF1*^{plus} patients (46.6 ± 9.9% vs 60.6 ± 14.0%, $p = 0.67$; 78.7 ± 8.5% vs 93.8 ± 6.1%, $p = 0.89$) indicating that also *IKZF1*^{plus} has no predictive value (Supplementary Fig. S1C).

Given that patients were enrolled in various clinical trials with differing risk stratification criteria and treatment regimens, we compared the outcomes between earlier clinical trials and the two most contemporary ones (i.e., AIEOP-BFM ALL 2017, ALLTogether-1) but did not find any significant improvement (Supplementary Fig. S1D).

When comparing the outcomes of children and infants, we observed a higher CIR and consequently a poorer EFS for infant patients (Supplementary Fig. S2A). As several patients were just over 1 year of age (Table 1), we explored whether age influenced the outcome. Our analysis according to different age groups revealed that patients aged <18 months had a significantly higher 5-year CIR (68.5 ± 12.7% vs 36.2 ± 9.4%, $p = 0.006$) and worse outcome (Fig. 1C) than other age groups (Supplementary Figs. S2B–D). In multivariate analysis, EOI-MRD $\geq 5 \times 10^{-4}$ (hazard ratio 15.55, $p = 0.001$) and age (<18 months vs older; hazard ratio 16.65, $p = 0.001$) had an independent impact on EFS (Fig. 1D).

Collectively, our study demonstrates that childhood *PAX5*::*AUTS2* B-ALL is characterized by a high frequency of CNS involvement and is a relapse-prone subtype with poor outcomes. The disease mainly affects infants and toddlers with over 80% being less than three years old, which differs from the childhood *PAX5*alt group, which is more common in older patients (children 1–18 years, $n = 94$, median 9.5 years; ST1 cohort [1]) [1, 8, 9]. The observed EFS and OS survival rates for *PAX5*::*AUTS2* B-ALL were lower than those in the overall *PAX5*alt group but similar to those of patients with *PAX5*^{AMP} [1, 8, 9, 11], underlining the importance of focusing outcome analysis on genetically homogeneous entities with unique alterations.

Our data also support the notion that *PAX5*-r is in general recurrent in infants and along with *KMT2A*-r may represent a further subgroup of infant B-ALL with a potentially dismal outcome, while *NUTM1*-r has a favorable prognosis [6, 7, 13].

The finding that *PAX5*::*AUTS2* patients enrolled in contemporary trials still exhibit high relapse rates, emphasizes the need to further explore innovative targeted treatment options [3]. Moreover, strategies to mitigate the risk of relapse and treatment-related mortality associated with salvage therapy are needed. Frontline use of the bi-specific T-cell engager blinatumomab, which has been proven to be safe and effective also in infants [14, 15] may be a worthwhile consideration.

DATA AVAILABILITY

The data relevant to this study are provided in Supplementary Table S1. More detailed de-identified patient and genetic data may only be obtained from the relevant clinical trial committees upon reasonable request.

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AUTHOR CONTRIBUTIONS

SS conceived the study, coordinated the data collection, analyzed data, and wrote the manuscript; ACE, GF, AP, JMB, DS, DG, ES, LD, JB, BAL, MZ, GE, IS, ME, JT, LC, MP, AVM, AKB, MLB, WM, GC, and HC contributed genetic and clinical patient data; SH, AI, and KN analyzed, reviewed and interpreted SNP array data; MK, performed FISH analysis and interpreted data; KF conducted molecular genetic analysis of patient samples; DS interpreted data and conducted outcome analysis. All authors reviewed and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the ethical standards of the institutional and/or national research committees and with the ethical standards as laid down in the Declaration of Helsinki, and all methods were performed in accordance with the relevant guidelines and regulations. Patients were enrolled in an approved international or national clinical trial with written informed consent from their parents or legal guardians. The institutional review boards of the participating study groups approved the use of anonymized patient data for research purposes.

ADDITIONAL INFORMATION

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