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Jenifer Vaughan; Nikki Bouwer; Pascale Willem; Tracey Wiggill; Katherine Hodkinson

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SA Journal of Oncology
ISSN: (Online) 2523-0646, (Print) 2518-8704

The translocation t(1;19)(q23;p13) (TCF3/PBX1 fusion) is the most common recurrent genetic abnormality detected amongst patients with B-cell lymphoblastic leukaemia in Johannesburg, South Africa

Authors:
Jenifer Vaughan[1,2]
Nikki Bouwer[1,3]
Pascale Willem[1,3]
Tracey Wiggill[1,3]
Katherine Hodkinson[1,3]

Affiliations:
[1]Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[2]Department of Molecular Medicine and Haematology, Chris Hani Baragwanath Academic Hospital, National Health Laboratory Services, Johannesburg, South Africa

[3]Department of Molecular Medicine and Haematology, Charlotte Maxeke Johannesburg Academic Hospital, National Health Laboratory Services, Johannesburg, South Africa

Corresponding author:
Jenifer Vaughan,
jenifer.vaughan@nhls.ac.za

Dates:
Received: 30 Mar. 2021
Accepted: 17 May 2021
Published: 06 July 2021

How to cite this article:
Vaughan J, Bouwer N, Willem P, Wiggill T, Hodkinson K. The translocation t(1;19)(q23;p13) (TCF3/PBX1 fusion) is the most common recurrent genetic abnormality detected amongst patients with B-cell lymphoblastic leukaemia in Johannesburg, South Africa. S. Afr. j. oncol. 2021;5(0), a179. https://doi.org/10.4102/sajo.v5i0.179

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Background: B-cell lymphoblastic leukaemia (B-ALL) is a malignancy of immature B-cells with several described recurrent genetic abnormalities. These have distinct clinico-pathological associations and show regional variation in prevalence. In all previously reported series, the translocation t(1;19) is uncommon, comprising < 10% of all cases. The genetic composition of B-ALL in Africa is unknown.

Aim: The aim of this study was to assess the genetic landscape of B-ALL in Johannesburg, South Africa.

Setting: The Johannesburg state-sector.

Methods: All cases of B-ALL diagnosed by flow cytometry in the state-sector hospitals of Johannesburg over 36 months between 2016 and 2019 were identified and pertinent data were recorded from the laboratory information system.

Results: A total of 108 patients with B-ALL were identified, 82 (75.9%) of whom were children or adolescents. The translocation t(1;19)(q23;p13) was the most common genetic abnormality identified (23.7% of cases), predominating in young patients. The translocation t(9;22)(q34;q11) was the next most common aberration (17.5%) occurring predominantly in adults > 40 years of age, but also in 8.1% of children. Crude survival rates were overall poor (44.6% overall and 57.4% in patients < 18 years of age). On survival analysis, older age, KMT2A-rearrangement and t(1;19) were independently associated with relapse-related death. The t(9;22) was not associated with mortality independently from age.

Conclusion: B-ALL shows a distinct pattern of lymphoblastic leukaemia-associated chromosomal translocations in Johannesburg.

Keywords: B-cell acute lymphoblastic leukaemia; genetics; t(1;19); South Africa; epidemiology.

Introduction

Lymphoblastic leukaemia (ALL) is a neoplasm of immature lymphocytes of either B- or T-cell lineage. It is the most common malignancy encountered in childhood, but can occur at any age. The World Health Organization's (WHO) classification of tumours of haemopoietic and lymphoid tissues recognises several recurrent chromosomal translocations in B-cell ALL (B-ALL),[1] including the translocation t(12;21)(p13;q22)(t(12;21)), the translocation t(1;19)(q23;p13)(t(1;19)), the translocation t(9;22)(q34;q11)(t(9;22)), rearrangement of the KMT2A gene and hyperdiploidy. These have well-documented clinical and prognostic associations and require differing therapeutic strategies (Table 1). Other important negative prognostic factors included patient age (> 10 years), presenting white cell count (> 50 × 10^9/L) and the presence of measurable residual disease (MRD) (> 0.01% – 0.1%) following induction chemotherapy. The genetic landscape of B-ALL shows regional variation, with the t(12;21) and hyperdiploidy predominating amongst childhood B-ALL in Europe and the United States of America,[2,3,4,5] and KMT2A-rearrangement and t(9;22) being relatively more common in Asia.[6,7] In all reported series, the t(1;19) is uncommon, occurring more frequently in childhood, but comprising < 10% of all cases.[2,4,5,6,7,8] The genetic composition of B-ALL encountered in Africa is not known. This observational study aimed to assess the frequency of these genetic aberrations, along with

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TABLE 1: Common recurrent genetic abnormalities seen in B-cell lymphoblastic leukaemia.

Genetic abnormality	Typical age and other clinical associations	Prognostic impact	Therapeutic implication
t(12;21)	Almost exclusively seen in childhood. Relapses occur later than in other subtypes of ALL.	Favourable	Requires standard risk treatment
t(9;22)	Can occur at any age, but occurs with increasing frequency with increasing age	Historically poor, improved in the era of tyrosine kinase inhibitor therapy	Requires high-risk treatment together with a tyrosine kinase inhibitor
Hyperdiploidy	More common in childhood	Favourable	Requires standard risk treatment
Rearrangement of the KMT2A gene	More common in infants and adults The WCC is often markedly elevated (> 100 × 10^9/L), and CNS involvement at diagnosis is more common.	Unfavourable	Requires high-risk treatment
t(1;19)	More common in childhood. May have an increased risk of isolated CNS relapse.	Intermediate	Unclear

Source: Stein H, Campo E, Harris NL. WHO classification of tumors of the haematopoietic and lymphoid tissues. Lyon: IARC; 2017

ALL, acute lymphoblastic leukaemia; WCC, white cell count; CNS, central nervous system.

selected clinico-pathological features in B-ALL diagnosed in Johannesburg, South Africa (SA).

Methods

Cases were identified from the register of specimens analysed by the flow cytometry laboratory at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over a 36-month period between 2016 and 2019. This laboratory provides diagnostic immunophenotyping services to all state-sector hospitals of the southern Gauteng region of South Africa. All samples with a diagnosis of acute leukaemia were recorded in a database, and pertinent information was documented from the laboratory information system (LIS) (TrakCare, InterSystems, Cambridge, Massachusetts, United States [US]) (including available clinical information, peripheral blood counts, immunophenotypic findings of interest, cytogenetic/fluorescence *in situ* hybridisation [FISH] results, final diagnosis [as per the 2017 WHO classification], cerebrospinal fluid [CSF] cytology, therapy responses, survival time and cause of death [where apparent]). Cases of B-ALL were then extracted from the database and analysed. Measurable residual disease in the bone marrow following induction chemotherapy was defined on flow cytometry as a discrete population of cells with the leukaemia-associated immunophenotype and/or on polymerase chain reaction (PCR) analysis of immunoglobin heavy gene rearrangement status (IdentiClone IGH Gene Clonality Assay; Invivoscribe, San Diego, California, US), as a monoclonal product of the same size as that documented at presentation. Central nervous system (CNS) involvement was defined on the basis of the detection of blasts in the CSF on microscopy and/or flow cytometry.

Statistical analysis

Continuous data are presented as the median (interquartile range [IQR]) and categorical data as frequencies and percentages. The Mann–Whitney U-test and Fisher's exact test were used to compare continuous and ordinal variables of interest, respectively. A Cox proportional-hazards model was used to investigate the association between the survival time and predictor variables of interest (namely age > 10 years, WCC > 50 × 10^9/L and the presence of recurrent genetic abnormalities (t(1;19), t(9;22), t(12;21), KMT2A rearrangement or hyperdiploidy) ± MRD status). Statistical analysis was performed using Prism software, version 5 (GraphPad Software, San Diego, California, US) and at https://statpages.info/prophaz.html (for Cox proportional-hazard regression analysis). Statistical significance was accepted at a two-sided *p*-value of < 0.05.

Results

Acute leukaemia was diagnosed in 461 cases over the time period assessed, of which B-ALL made up 23.4% (108 cases). The median patient age was 8 years (range 3 months to 79 years) (Table 2), with 82 (75.9%) cases being diagnosed in patients ≤ 18 years of age. The majority of cases (93.5%) expressed a precursor B-cell/common immunophenotype, and 4 (3.7%) represented blast-phase transformation of underlying chronic myeloid leukaemia. Human immunodeficiency virus (HIV)-status was documented in 67 patients, only one of whom was HIV-positive. Documented involvement of the CNS was uncommon, occurring in three patients at presentation and in five at disease relapse. Pertinent demographic and laboratory data are summarised in Table 2.

The t(1;19) was the most common recurrent genetic abnormality identified, occurring in 23.7% of cases (Table 2). It predominated in children, was the dominant recurrent abnormality encountered in adolescents and the second most common seen in adults < 40 years of age (Figure 1). All cases of t(1;19) expressed a precursor B-cell/common immunophenotype and they were CD34-negative in 20/23 (87.0%) cases. The sensitivity and specificity of CD34-negativity for the detection of t(1;19) was 87% and 75%, respectively. Amongst patients with available data, 11/15 (73.3%) achieved a molecular remission post-induction chemotherapy, whilst the remaining patients had MRD. Central nervous system disease was documented in one patient with t(1;19) at presentation and only one patient with t(1;19) experienced a CNS relapse (with accompanying medullary disease).

The t(9;22) was the next most common abnormality encountered (17.5% of cases), occurring broadly across most age ranges and particularly predominating in adults > 40 years of age. Amongst children < 18 years of age, the t(9;22) was present in 8.1% of those tested. Amongst patients with available MRD data, 3/7 (42.2%) achieved a molecular remission post-induction chemotherapy, whilst the remaining patients had MRD. The t(12;21) occurred exclusively in children ≤ 10 years of age and occurred with equal frequency to the t(1;19) in this age range (24.1%). Amongst patients with available MRD data, only 1/11 (9.1%) had MRD post-induction. Hyperdiploidy was seen solely in patients ≤ 14 years of age, with a peak in children aged 2–10

years where it comprised 17.3% of all cases. Post-induction MRD was detected in 2/9 (22.2%) of these cases.

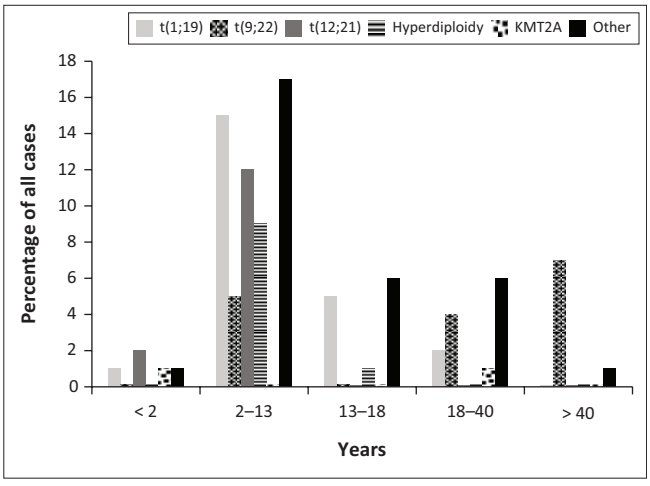
TABLE 2: Pertinent demographic and laboratory information in patients with B-cell acute lymphoblastic leukaemia.

Parameter	*n*	%	Median	IQR
Gender	-	-	-	-
Male	50	46.3	-	-
Female	58	53.7	-	-
Age (years)	-	-	8	4–18
Age ≤ 18	82	78.1	-	-
Age > 18	26	24.1	-	-
Age 15–39	25	23.1	-	-
Age ≥ 40	9	8.3	-	-
Hb (g/dl)	-	-	6.8	5.0–8.3¶
Plts (× 10^9/L)	-	-	32	18–73¶
WCC (× 10^9/L)	-	-	15.8	4.6–61.9¶
Neutrophils (× 10^9/l)	-	-	0.96	0.25–3.12¶¶
Peripheral blood blast count (%)	-	-	61	18–88†††
Documented CNS disease at presentation	3	3.7††	-	-
Documented CNS relapse	5	7.7‡‡	-	-
Immunophenotype	-	-	-	-
Pre-B/common	101	93.5	-	-
Null	3	2.8	-	-
Mature†	2	1.9	-	-
Unclassifiable	2	1.9	-	-
Recurrent cytogenetic abnormalities	67§	69.1	-	-
t(12;21)	14§	14.4	-	-
t(9;22)	17§	17.5	-	-
t(1;19)§§	23§	23.7	-	-
KMT2A rearrangement	3§	3.1	-	-
Hyperdiploidy‡	10§	10.3	-	-

Male to female ratio, 0.86:1.

Hb, haemoglobin; Plts, platelets; WCC, white cell count; CNS, central nervous system; IQR, interquartile range.

†, Mature immunophenotype refers to cases with surface light chain expression with other markers of immaturity; ‡, Patients were defined as having hyperdiploidy on the basis of karyotypic findings in all cases with the exception of a single child who had extra copies of chromosomes 1, 9, 12, 19, 21 and 22 on fluorescence *in situ* hybridisation (FISH) analysis with an unsuccessful karyotype; §, N = 97; all but two of these patients had cytogenetic analysis and/or FISH analysis for t(9;22), t(1;19), t(12;21) and KMT2A rearrangement performed. In the remaining two patients, cytogenetic results were not available, and results for FISH analysis were available only for the t(9;22) and t(12;21)/t(9;22) and t(1;19), respectively; ¶, N = 104; ††, N = 82; ‡‡, N = 65. Cytogenetic analysis was performed in 85 patients, but was unsuccessful in 15 of these; §§, The t(1;19) was unbalanced in 18 (78.3%) cases. A karyotype was available in 15 of the patients with t(1;19) and showed additional cytogenetic abnormalities in 7 (46.7%) of these; ¶¶, N = 101; †††, N = 95.



Note: 'Other' cases include those with other genetic abnormalities or a normal karyotype.

FIGURE 1: The distribution of genetic abnormalities in B-cell lymphoblastic leukaemia according to age categories, presented as a percentage of all cases (N = 97).

Crude survival data were available in 83 patients, with a median follow-up period of 34.5 months. A total of 46 (55.4%) of the patients had demised at the time of data collection (including 14/42 [33.3%] of the children < 10 years of age and 12/19 [63.2%] of the patients aged 10–18 years). Survival rates at 6-months and 1-year were good amongst patients with t(12;21) and hyperdiploidy, but appeared substantially poorer amongst those with t(9;22), t(1;19) and KMT2A-rearrangement (Table 3). However, on Cox proportional-hazard analysis of all-cause mortality, the only factors independently and significantly associated with mortality were age > 10 years and KMT2A-rearrangement (Table 3). Amongst the patients who demised, 19 (41.3%) died from sepsis as a complication of severe chemotherapy-related neutropenia and 18 (39.1%) died because of disease-relapse (detailed in Table 3). The cause of death was not evident from the laboratory records in the remaining patients. The t(1;19) was the most common genetic abnormality identified amongst the patients who died because of relapse, occurring in 7 (38.9%) cases (Table 3). On Cox proportional-hazard analysis of relapse-related mortality, age > 10 years, KMT2A-rearrangement and t(1;19) were confirmed to be independently associated with death because of relapse (Table 3). Amongst patients with t(1;19), there was no association between relapse-related mortality and the presence of an unbalanced t(1;19) or additional cytogenetic abnormalities.

Information with regard to both survival and MRD-status post-induction chemotherapy was available in 49 patients, of whom 13 (26.5%) had MRD. On Cox proportional-hazard analysis of these cases, MRD-positivity was found to be a significant predictor of relapse-related mortality, overarching the negative prognostic impact of both age and t(1;19), whilst KMT2A-positivity remained an independent risk factor for relapse (Table 3). Notably, the negative prognostic impact of MRD in patients with survival data was not present amongst the patients with t(9;22), of whom 4/6 (66.7%) had MRD post-induction, but only one of whom (16.7%) died because of relapse.

Children < 18 years of age were significantly less likely to die of sepsis as compared with adults (8/58 [13.8%], < 18 years versus 11/24 [45.8%], ≥ 18 years; p = 0.005), and age > 10 years was the only statistically significant risk factor for sepsis-related death on Cox proportional-hazard analysis (p = 0.004; data not shown). Amongst the children with available mortality data, sepsis-related mortality was particularly prominent in those with t(9;22) (3/6 [50%], as compared with 3/15 [20%] in those with t(1;19) and 2/35 [5.7%] in those with other abnormalities). In contrast, sepsis-related mortality was evenly distributed across all the genetic subgroups amongst adult patients (4/8 [50%] in t(9;22), 1/2 [50%] in t(1;19) and 6/13 [46.1%] in those with other genetic findings).

Discussion

In this observational study assessing the genetic composition and selected clinico-pathological characteristics of B-ALL

TABLE 3: Pertinent survival data.

Parameter	6-month survival rate			12-month survival rate			Cox proportional Hazard result All cause mortality			Cox proportional Hazard result Relapse-related mortality			Cox proportional Hazard result Relapse-related mortality in cases with MRD data			Death due to relapse		
	N	*n*	%	*N*	*n*	%	Co-efficient	Risk ratio	*p*	Co-efficient	Risk ratio	*p*	Co-efficient	Risk ratio	*p*	*N*	*n*	%
All patients	83	57	68.7	83	43	51.8	N/A	-	-	N/A	-	-	N/A	-	-	83	18	21.7
Age > 10 years	38	16	42.1	38	8	21.1	1.5	4.5	0.0002	2.4	11.1	0.003	1.60	4.9	0.11	36	9	25.0
WCC > 50 x109/L	23	16	69.6	23	11	47.8	-0.35	0.7	0.41	–0.77	0.5	0.24	–1.11	0.3	0.35	-	-	-
< 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	13	5	38.5
> 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10	2	20.0
t(9;22)	16	9	56.3	16	4	25.0	0.7	2.0	0.19	1.4	4.1	0.17	–0.04	0.96	0.98	-	-	-
< 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	0	0.0
> 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	3	37.5
t(1;19)	17	12	70.6	17	7	41.2	0.85	2.3	0.09	2.9	17.3	0.006	2.0	7.7	0.13	-	-	-
< 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15	6	40.0
> 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	1	50.0
t(12;21)	12	12	100.0	12	12	100.0	-1.4	0.26	0.21	0.6	1.8	0.65	–11.4	0.0	0.95	-	-	-
< 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12	1	8.3
> 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	N/A	N/A	N/A
Hyperdiploidy	8	8	100.0	8	6	75.0	-1.1	0.35	0.32	1.0	2.6	0.46	–0.08	0.9	0.96	-	-	-
< 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-		8	1	12.5
> 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-		N/A	N/A	N/A
KMT2A	3	2	66.0	3	1	33.0	1.6	5.0	0.022	4.7	115.2	0.0009	4.0	52.8	0.038	-	-	-
< 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	2	100.0
> 18 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0.0

MRD, measurable residual disease; WCC, white cell count; N/A, not applicable.

diagnosed in Johannesburg, South Africa, the most common recurrent genetic abnormality was found to be the t(1;19), which occurred in 23.7% of cases. This is in contrast to reports from other parts of the world, where this abnormality has been found to be uncommon (comprising between 2% – 5% and 4% – 7% in studies from the West[2,4,5,8] and Asia,[6,7] respectively). Notably, Pui et al. reported a higher frequency of the t(1;19) amongst African American children (11.8%)[4]; together with our findings, this suggests a particular predilection for this entity amongst individuals of African descent. As has been described previously, the t(1;19) was seen most frequently in children and adolescents,[9] but was also the second most common recurrent abnormality seen in adults between 18 and 40 years of age. It was not significantly associated with inferior disease outcomes on analysis of all-cause mortality, but was associated with an increased risk of death because of relapse. This was predominantly medullary in nature, with only one patient experiencing accompanying CNS relapse. This is in contrast to the findings of Jeha et al., who found haematological relapse to be rare amongst children with t(1;19), whilst isolated CNS relapse was more common.[10] Other reports have suggested that the t(1;19) is prognostically neutral if treated with contemporary intensive therapy protocols,[11,12,13,14] thus negating the need to identify this abnormality for risk stratification. Unfortunately, details on patient management were not universally available from the laboratory record in this study, but B-ALL with t(1;19) is routinely treated with high-risk protocols in the Johannesburg paediatric-oncology units. Our findings thus suggest that the t(1;19) is a negative prognostic marker in the South African setting (even when treated intensively), but further studies (including in-depth clinical and therapeutic data) are needed for confirmation in this regard. Nonetheless, routine testing for t(1;19) in South African patients with B-ALL is clearly warranted. CD34-negativity on the tumour population was associated with the t(1;19) (as has been reported previously),[15] with relatively high sensitivity (87%) and specificity (75%). Molecular testing for this entity should therefore be particularly prioritised in cases lacking CD34 expression in the South African setting.

The t(9;22) was the second most common abnormality detected, occurring predominantly in older adults (as reported previously).[9,16] Of note however was that the t(9;22) was detected in > 8% of children < 18 years of age, which is comparable with the frequency of this abnormality in childhood B-ALL in the Far East (~5% – 7%)[6,7] and amongst African Americans (5.9%),[4] and substantially higher than that generally seen in cohorts from Europe and the United States (~2%).[2,3,4,5,8] Although the t(9;22) has historically been regarded as a negative prognostic indicator, it was not significantly associated with an increased risk of mortality independently from age in this study. This is likely to be attributable to the routine use of tyrosine kinase inhibitors (TKIs) in combination with standard chemotherapy amongst these patients, which has been shown to ameliorate the negative impact of this abnormality.[16] However, it is notable that the children with t(9;22) in this study appeared to have an increased risk of death because of sepsis, possibly reflecting more marked myelosuppression as a result of the combined effects of intensive chemotherapy and TKIs in these patients. Sepsis was also a prominent cause of death across all the genetic subgroups amongst patients > 18 years of age, with age > 10 years being the only significant risk factor identified for sepsis-related mortality. These findings point to a need for

more intensive neutropenic support for children with t(9;22) and all adult patients in our setting.

Crude survival rates were substantially poorer in our series (< 50% overall and < 60% in patients < 18 years of age) as compared with those described in high-income countries, where cure rates using contemporary chemotherapy regimens have been reported to approach 90% in childhood ALL.[17] This was in spite of a relatively short median follow-up period (34.5 months), which suggests that long-term survival rates are likely to be even poorer. The reasons for the inferior survival rates are likely to be multifactorial, including the effects of socio-economic factors, suboptimal neutropenic support, a more limited armamentarium of therapeutic options (including allogeneic stem cell transplantation) in the Johannesburg state sector as well as differences in tumour and host biology. With regard to the latter, poorer outcomes are well described amongst patients of African descent, and this disparity was reported by Kirtane et al. to be greater in black children with ALL as compared with those with acute myeloid leukaemia (AML).[18] This suggests that the race-related differences in ALL outcomes are not solely attributable to non-biological factors, and that racial differences in tumour biology and/or drug metabolism are likely to be important. This may account for the poorer outcomes seen in the patients with t(1;19) in this study as compared with those reported in Europe, Asia and the United States of America,[4,11,12,13,14,19] although Pui et al. did not find inferior survival rates amongst African American children with t(1;19)-positive B-ALL as compared with their white counterparts. Deeper molecular investigation into differences in tumour genetics and pharmacogenomics amongst South African patients would be of interest.

Measurable residual disease testing performed in our centre over the time period of this study was fairly rudimentary, comprising non-quantitative, non-allele-specific PCR analysis of IgH gene rearrangement status and four colour flow cytometry (both with sensitivities > 0.1%). Despite this, the presence of MRD was significantly associated with death because of relapse independently of all other prognostic factors with the exception of KMT2A rearrangement. This highlights the value of MRD testing in the resource-constrained setting, even when state-of-the-art techniques are not available. Notably, the high risk of relapse-related mortality associated with MRD positivity was not seen in patients with t(9;22), likely because of the use of targeted molecular therapy in these patients. This emphasises the value of such drugs and the need for further research into therapies targeting other high-risk genetic lesions in ALL.

Conclusion

This observational study has demonstrated the t(1;19) to be a common genetic abnormality amongst South Africans with B-ALL. This appears to be associated with an increased risk of relapse-related mortality in our setting, but further studies including in-depth clinical and therapeutic data are required for confirmation in this regard. The t(9;22) also has an increased frequency amongst children with B-ALL as compared with patients in the West, but is not independently associated with mortality in our setting. Sepsis-related mortality is common, particularly in adult patients, thus suggesting a need for more intensive neutropenic support in the Johannesburg state sector.

Acknowledgements

The authors would like to acknowledge all the staff members of the following units for their invaluable contributions towards leukaemia diagnosis and management in the Johannesburg state sector:

- Flow cytometry laboratory at the CMJAH
- Somatic Cell Genetics unit at the CMJAH
- Morphology units of the CMJAH, the Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital
- Medical Oncology Unit at the CMJAH
- Paediatric oncology units at the CMJAH and CHBAH
- Clinical Haematology Unit at the CHBAH
- Cytology Unit in the Division of Anatomical Pathology at the University of the Witwatersrand.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

J.V. performed data collection, data analysis and wrote the manuscript. N.B. designed the study, obtained ethical approval and provided editorial support. T.W. and P.W. provided editorial input. K.H. performed data collection and also provided editorial input. All authors read and approved the final version of the manuscript.

Ethical considerations

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Protocol number: M150160).

Funding information

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data availability

The data that support the findings of this study are available from the corresponding author (J.V.) upon reasonable request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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