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

T-cell lymphoblastic leukaemia: The Johannesburg state-sector experience

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

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: 02 Mar. 2022
Accepted: 18 Apr. 2022
Published: 22 June 2022

How to cite this article:
Vaughan J, Wiggill T, Willem P, Hodkinson K. T-cell lymphoblastic leukaemia: The Johannesburg state-sector experience. S Afr j oncol 2022; 6(0), a229. https://doi.org/10.4102/sajo.v6i0.229

Background: T-cell lymphoblastic leukaemia (T-ALL) is a malignancy of immature T-cells which is reported to comprise 7% – 23% of cases of lymphoblastic leukaemia (ALL), making up a larger proportion of adult ALL than childhood cases. It is characterised by an increased risk for early relapse but reportedly has superior outcomes as compared to B-cell ALL amongst adult patients. The frequency and clinical behaviour of T-ALL in Africa are unknown.

Aim: This study aimed to assess the prevalence and selected clinicopathological features of T-ALL in Johannesburg, South Africa (SA).

Setting: The Johannesburg state sector.

Methods: All cases of ALL diagnosed by flow cytometry in the state-sector hospitals of Johannesburg over 42 months between 2016 and 2019 were identified and pertinent data recorded from the laboratory information system.

Results: One hundred and eighty-one cases of ALL were identified, of which 59 (32.6%) were of T-cell lineage. The proportion of adult and paediatric ALL made up by T-ALL was similar (19/54 [35.2%] vs 40/127 [31.5%] respectively). Crude survival rates were very poor, with 80.0% having demised at the time of data collection. The mortality rate was overall significantly poorer amongst patients with T-ALL (80.0%) as compared to those with B-ALL (53.8%; $p = 0.005$) but was similarly poor in adults with B-ALL (83.3%) vs T-ALL (86.7%) ($p = 0.53$). The mortality rate did not differ between those with low-risk versus high-risk clinical features (77.8% vs 80.6%; $p = 1.00$).

Conclusion: T-cell lymphoblastic leukaemia makes up a larger proportion of ALL in Johannesburg than is reported elsewhere, and it is a high-risk disease that is not well stratified by conventional risk factors.

Keywords: T-cell lymphoblastic leukaemia; South Africa; epidemiology; ALL; T-ALL.

Introduction

Lymphoblastic leukaemia (ALL) is a malignancy of immature lymphocytes involving the peripheral blood and bone marrow. It is subdivided into B-cell and T-cell subtypes, of which B-cell ALL (B-ALL) is the more common. B-ALL is characterised by a number of recurrent genetic abnormalities, which have distinct clinicopathological associations. In contrast, T-cell ALL (T-ALL) is a genetically heterogeneous disease without clear prognostic associations with any particular genetic subtype. T-ALL occurs in all age groups, but reportedly comprises a larger proportion of adult lymphoblastic leukaemia (~18% – 23%)[1,2] than childhood cases (~7% – 15%).[3,4,5,6,7,8,9] It is characterised clinically by a propensity for mediastinal involvement (often with an associated pleural effusion) and an increased risk for both early relapse and isolated relapse in the central nervous system (CNS).[10] Hyperleukocytosis is common, typically with relative sparing of the haemoglobin, platelet and neutrophil counts.[10] Reported prognostic determinants in T-ALL include the early therapy response, white cell count (WCC) ($> 100 \times 10^9$/L), the presence of a complex karyotype (≥ 5 chromosomal abnormalities)[2] and, to a lesser extent, the immunophenotype (superior in CD1a positive and CD13 negative cases).[2] Children with T-ALL more frequently have high-risk clinical features (age: > 10 years, WCC: $> 50 \times 10^9$/L) than those with B-ALL, but they reportedly have similar outcomes as compared to high-risk B-ALL when treated with intensive therapy protocols.[8] In contrast, children with T-ALL without high-risk features tend to have somewhat inferior outcomes as compared to standard-risk B-ALL.[8] Outcomes in adult T-ALL are slightly superior to B-ALL,[1,11] possibly because of the high frequency of high-risk genetic abnormalities amongst older individuals with B-ALL. The frequency of T-ALL shows some regional variation, being lowest in Asia (~7% of childhood cases)[3] and substantially higher amongst African-Americans (~25%).[12,13] We have previously reported on the frequency and cytogenetic landscape of B-ALL in South Africa (SA),[14]

but to date, there is very little reported data regarding T-ALL in Africa. This study aimed to assess the prevalence and selected clinicopathological features of T-ALL diagnosed in the state sector of Johannesburg, South Africa.

Methods

Cases were identified through the specimen register in the flow cytometry laboratory at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over a 42-month period between 2016 and 2019. This laboratory provides diagnostic immunophenotyping services to all state-sector hospitals of the southern Gauteng region of SA. All cases with a diagnosis of acute leukaemia were identified and recorded in a database, and pertinent information was documented from the laboratory information system (TrakCare, InterSystems, Cambridge, Massachusetts, United States), including available clinical information, peripheral blood counts, immunophenotypic findings of interest, cytogenetic and/or fluorescence *in situ* hybridisation (FISH) results, cerebrospinal fluid (CSF) cytology, final diagnosis (as per the 2017 World Health Organization (WHO) classification), therapy responses, survival time and cause of death (where apparent). Cases of T-ALL were then extracted from the database and analysed. Where appropriate, comparison was made with patients with B-ALL (which we have reported previously).[14] High-risk clinical features were defined as age > 10 years and/or WCC > 50×10^9/L for patients with B-ALL, as well as age > 10 years and/or WCC > 100×10^9/L for those with T-ALL. Patients with a cortical thymocyte immunophenotype on only a subpopulation of the tumour cells were classified as expressing a cortical thymocyte immunophenotype. Measurable residual disease (MRD) in the bone marrow following chemotherapy (postinduction and on approximately day 76) was defined on flow cytometry as a discrete population of cells with the leukaemia-associated immunophenotype and/or on polymerase chain reaction analysis of T-cell receptor (TCR) gene rearrangement status (IdentiClone™ TCRG Gene Clonality Assay for T-cell gene rearrangements: version 1 kit assay [InVivoScribe Technologies; San Diego, California, United States]) as a monoclonal product of a similar size as that documented at presentation or as a new reproducible and consistent monoclonal product. Central nervous system 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) 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 > 100×10^9/L, male gender, a cortical thymocyte immunophenotype and the presence of aberrant CD13 expression). Statistical analysis was performed using Prism software, version 5 (GraphPad Software, San Diego, California, United States) 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.

Ethical considerations

This study was approved by the Human Research Ethics committee of the University of the Witwatersrand (protocol number: M150160, 24 July 2019).

Results

ALL was diagnosed in 181 cases over the time-period assessed, of which T-ALL made up 32.6% (59 cases). The median patient age in T-ALL was 12 years (ranging from 1 to 59 years) (Table 1), with 40 (67.8%) cases being diagnosed in patients < 18 years of age. The proportion of adult and paediatric (< 18 years) ALL made up by T-ALL was similar (19/54 [35.2%] vs 40/127 [31.5%] respectively). The majority of cases (72.9%) occurred in male patients, with a more marked male predominance amongst adult patients (84.2%). Documented mediastinal involvement was common (44.9% of cases), as were the presence of hepatosplenomegaly (36.7%) and lymphadenopathy (69.1%). As compared to patients with B-ALL, male gender, lymphadenopathy and mediastinal involvement were significantly more common in T-ALL, whilst there was no significant difference in patient age, the presence of hepatosplenomegaly or CNS involvement (Table 1). Although the median peripheral blood blast percentage was similar at presentation in patients with T-ALL as compared to those with B-ALL, the patients with T-ALL had significantly higher WCCs, haemoglobin levels, platelet counts and neutrophil counts (Table 1). High-risk clinical features were significantly more frequent amongst patients with T-ALL as compared to those with B-ALL, being present in 48 (81.4%) patients overall (as compared to 56.3% of those with B-ALL; $p = 0.001$) and 11 (52.4%) of the patients < 10 years of age (versus 14.0% of the children with B-ALL; $p < 0.0001$). HIV test results were available in 40 patients; all but two of whom were HIV negative. Pertinent demographic, clinical and laboratory data for the patients with T-ALL as compared to those with B-ALL are summarised in Table 1.

With respect to the immunophenotypic subclassification, the cortical thymocyte subtype was the most common (Table 1); this predominated in children, whilst the pre-T-cell, cortical thymocyte and early T-precursor subtypes occurred with equal frequencies amongst the adults (Figure 1). Aberrant myeloid antigen expression was detected in 57.7% of the patients tested for myeloid antigens ($N = 52$), with 42.3% of the cases demonstrating aberrant CD13 expression. The latter was seen in all the immunophenotypic subtypes but was most common in the early T-precursor group (77.8%) and most infrequent in the cortical thymocyte group (17.2%).

Of patients who had a successful karyotype, 32/42 (76.2%) had one or more cytogenetic abnormality; a further two

TABLE 1: Pertinent demographic and laboratory information in patients with T-cell lymphoblastic leukaemia as compared to those with B-ALL.

Parameter	T-ALL						B-ALL						*p*
	Ratio	*N*	*n*	%	Median	IQR	Ratio	*N*	*n*	%	Median	IQR	
Male to female ratio overall	2.7:1	-	-	-	-	-	0.82:1	-	-	-	-	-	-
Males	-	43	-	72.9	-	-	-	55	-	45.1	-	-	**0.0008**
Male to female ratio < 18 years	2.1:1	-	-	-	-	-	0.89:1	-	-	-	-	-	-
Males < 18 years	-	27	-	67.5	-	-	0.67:1	41	-	47.1	-	-	**0.037**
Male to female ratio ≥ 18 years	5.3:1	-	-	-	-	-	-	-	-	-	-	-	-
Males ≥ 18 years	-	16	-	84.2	-	-	-	14	-	40.0	-	-	**0.005**
Age (years)	-	-	-	-	12	6–23	-	-	-	-	9.5	4–20.5	0.2
Age < 10 years	-	21	-	35.6	-	-	-	61	-	50.0	-	-	0.08
Age < 18 years	-	40	-	67.8	-	-	-	87	-	71.3	-	-	0.73
Age ≥ 18 years	-	19	-	32.2	-	-	-	35	-	28.7	-	-	0.73
Age 15–39 years	-	17	-	28.8	-	-	-	28	-	23.0	-	-	0.46
Age ≥ 40 years	-	4	-	6.8	-	-	-	12	-	9.8	-	-	0.59
Hb (g/dL)	-	-	-	-	8.7	6.6–11.5	-	-	-	-	6.8	5.0–8.3	**< 0.0001**
Plts ($\times 10^9$/L)	-	-	-	-	83	32–210	-	-	-	-	32	18–73	**0.0003**
WCC ($\times 10^9$/L)	-	-	-	-	41.7	11.2–203.0	-	-	-	-	15.8	4.6–61.9	**0.019**
WCC > 100×10^9/L	-	52	16	30.8	-	-	-	118	14	11.9	-	-	**0.004**
WCC > 400×10^9/L	-	52	6	11.5	-	-	-	118	0	0.0	-	-	**0.0007**
Neutrophils ($\times 10^9$/L)	-	-	-	-	5.42	0.87–9.59	-	-	-	-	0.96	0.25–3.12	**0.0008**
Peripheral blood blast count	-	-	-	-	50	16–84†	-	-	-	-	61	18–88	0.31
Documented mediastinal involvement	-	49	22	44.9	-	-	-	101	1	0.9	-	-	**< 0.0001**
Documented lymphadenopathy	-	49	34	69.4	-	-	-	101	50	49.5	-	-	0.02
Documented hepatosplenomegaly	-	49	18	36.7	-	-	-	101	34	33.7	-	-	0.7
Documented CNS involvement at presentation	-	46	3	6.5	-	-	-	92	3	3.3	-	-	0.66
Documented CNS relapse	-	43	4	9.3	-	-	-	80	6	7.5	-	-	0.74
Documented HIV positive	-	40	2	5.0	-	-	-	73	1	1.4	-	-	0.55
Immunophenotype													
Pre-T	-	9	-	15.3	-	-	-	N/A	N/A	N/A	-	-	-
Cortical thymocyte‡	-	29	-	49.2	-	-	-	N/A	N/A	N/A	-	-	-
Late	-	6	-	10.2	-	-	-	N/A	N/A	N/A	-	-	-
Early T-precursor	-	9	-	15.3	-	-	-	N/A	N/A	N/A	-	-	-
Mixed	-	2	-	3.4	-	-	-	N/A	N/A	N/A	-	-	-
Unclear	-	2	-	3.4	-	-	-	N/A	N/A	N/A	-	-	-

Note: *P*-value in bold is statistically significant.

T-ALL, T-cell lymphoblastic leukaemia; B-ALL, B-cell lymphoblastic leukaemia; CNS, central nervous system; N/A, not applicable; IQR, interquartile range; WCC, white cell count.

†, $N = 57$. ‡, Twelve of these patents expressed a cortical thymocyte immunophenotype on only a subpopulation of their blasts.

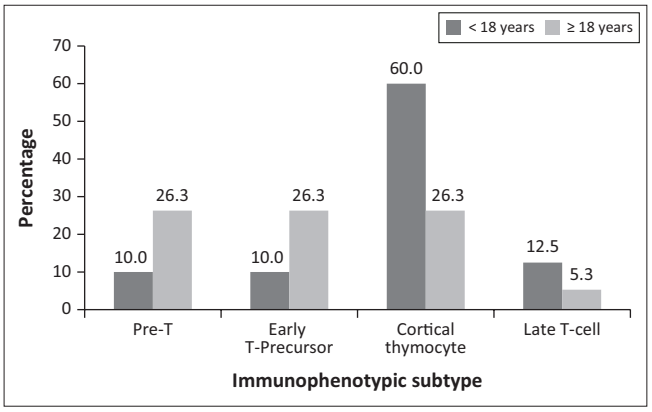

FIGURE 1: The distribution of immunophenotypic subtypes in T-cell lymphoblastic leukaemia according to age categories, presented as a percentage of cases in each age subgroup.

patients had the translocation t(9;22)(q34;q11) detected on FISH analysis. The most common were deletions or translocations involving the long arm of chromosome 6, translocations involving the TCR loci (α, β or δ), deletion of chromosome 9p and near tetraploidy. The translocation t(9;22) occurred in three of the tested patients, two of whom had T-lineage blastic transformation of pre-existing chronic myeloid leukaemia. The translocation t(10;11) (PICALM-MLLT10) and abnormalities involving the TLX1 (HOX11) and TLX3 (HOX 11L2) genes (which are amongst the most common genetic abnormalities reported in the international literature) were all infrequent, each occurring in only one patient in this cohort (Table 2). Two patients had a translocation involving chromosomes 6 and 12, one with breakpoints at (q?21;p?11.2) and the other at (q?23;p13). Notably, a breakpoint encompassing 6q21 was involved in seven of the eight cases (87.5%) with an abnormality of chromosome 6q.

Crude survival data was available in 45 patients, with a median follow-up period of 37 months. Twenty (44.4%) patients were alive one year after diagnosis, and 35 (77.8%) had died at the time of data collection (including 13/18 (72.2%) of the children < 10 years of age, 9/12 (75%) of the patients aged 10–18 years and 13/15 (86.7%) of the adults). The mortality rate did not differ between those with low-risk versus high-risk clinical features (77.8% vs 77.8%; $p = 1.00$) and was significantly poorer amongst patients with T-ALL (77.8%) as compared to those with B-ALL (50/93 (53.8%);

$p = 0.01$). The cause of death was evident from the laboratory records in 29 patients, of whom 16 (55.2%) died of disease relapse and 13 (44.8%) died from sepsis as a result of severe chemotherapy-associated neutropenia. Amongst patients with a known cause of death, death because of relapse did not occur significantly more frequently in patients with T-ALL as compared to those with B-ALL (55.2% vs 48.6%; $p = 0.6$). Central nervous system relapse occurred with similar frequency to that seen in B-ALL (4/39 [10.3%] in T-ALL vs 6/80 7.5% in B-ALL; $p = 0.73$), with half of the cases with CNS relapse having accompanying medullary disease. Amongst children < 10 years with T-ALL with and without high-risk features, there was no significant difference in the rate of relapse-related death (3/9 [33.3%] vs 5/9 [55.6%]; $p = 0.64$). Death because of relapse occurred significantly more frequently in children with T-ALL without high-risk features as compared to those with standard-risk B-ALL (5/9 [55.6%] vs 7/39 [17.9%], $p = 0.03$). In contrast, the rate of relapse-related death in children with high-risk clinical features (B-ALL versus T-ALL) did not differ statistically (1/4 (25%) vs 3/9 (33.3%); $p = 1.00$). In adult patients, the mortality rate was similarly poor in T-ALL (13/15, 86.7%) vs B-ALL (25/30, 83.3%) ($p = 0.53$), with 33.3% and 23.3% of deaths being attributable to disease relapse in T-cell and B-cell cases, respectively ($p = 0.72$). With respect to the prognostic impact of the immunophenotype, survival rates appeared to be superior in CD1a-positive cases (7/19 [36.8%]) and poorer in those expressing aberrant CD13 (1/16 [6.3%]). These findings lacked statistical significance ($p = 0.06$ and 0.11, respectively), however, possibly because of the limited sample size. However, on Cox proportional hazard analysis, the presence of a cortical thymocyte immunophenotype and aberrant CD13 expression were found to have significant independent associations with all-cause mortality, whilst only the presence of a cortical thymocyte immunophenotype was marginally associated with a reduced risk of relapse-related mortality (Table 3). Exhaustive analysis as regards the impact of the tumour karyotype on survival was not possible owing to the heterogeneous nature of the cytogenetic abnormalities observed. However, mortality rates amongst patients with abnormalities of the long arm of chromosome 6 did not differ significantly from those with other karyotypic findings (85.7% vs 77.8%; $p = 1.00$).

TABLE 2: Details of the cytogenetic results.

Karyotypic abnormality	Results in this cohort	Reported frequency in the international literature
Any cytogenetic abnormality on karyotyping (%)	76.2†	50[15]–70[16]
Abnormality of chromosome 6q (%)	19.0†	20–30[15]
Children (%)	26.7¶	10–20[17,18]
Adults (%)	0.0††	15–18[16]
Deletion of 9p (%)	9.5†	15[15,16]
Near tetraploidy (%)	9.5†	5[15]
Translocations involving TCR loci (14q11 [TCRα/δ] and 7q34 [TCRβ])	11.9†	35[15]
t(9;22) (%)	6.3‡	1[15]
KMT2A rearrangement (%)	5.9§	8[15]
LMO1 gene abnormalities (%)	7.1†	2[15]
TLX1 (HOX11) gene abnormalities (%)	2.4†	5–10[16]
Children (%)	3.3¶	7[15]
Adults (%)	0.0††	30[15]
TLX3 (HOX11L2) gene abnormalities (%)	2.4†	-
Children (%)	0.0¶	20[15]
Adults (%)	8.3††	10–15[15]
t(10;11) (PICALM-MLLT10) (%)	2.4†	10[15]
Complex karyotype	2.4†	-
t(1;14)/t(1;7) (involving the TAL1 gene)	0.0†	3[15]

TCR, T-cell receptor.
†, $N = 42$. ‡, $N = 48$. §, $N = 51$. ¶, $N = 30$. ††, $N = 12$.

Definitive MRD data was available in 32 (54.2%) patients postinduction, and in 11 (18.6%) patients around day 76. MRD was detected in 62.5% and 54.5% of the patients at each time point respectively. The 12-month survival rates were significantly lower in patients with MRD postinduction as compared to those without MRD at this time point (37.5% versus 81.8%; $p = 0.047$), with 60% of the MRD+ patients who demised within 12 months dying of early disease relapse. There was no significant difference in either the overall crude all-cause ($p = 0.2$) or the relapse-related ($p = 0.7$) mortality rates according to MRD status postinduction. In patients with and without MRD around day 76, there was no significant difference in the 12-month survival rate (60.0% [MRD-negative] vs 33.3% [MRD+]; $p = 0.57$), the all-cause mortality rate (60.0% [MRD-negative] vs 83.3% [MRD+]; $p = 0.54$) or the relapse-related mortality rate (40.0% [MRD-negative] vs 50.0% [MRD+]; $p = 1$), possibly in part because of the small sample size. Unfortunately, the small number of patients with both MRD and survival data precluded meaningful analysis of the independent risk of mortality associated with MRD in multivariate analysis. As compared to B-ALL, MRD was detected postinduction significantly more frequently in T-ALL (62.5% [T-ALL] vs 23.9% [B-ALL]; $p = 0.0003$).

TABLE 3: Pertinent survival data.

Parameter	6-month survival rate			12-month survival rate			Survival at the time of data collection†			Death because of relapse			Cox proportional hazard result; all cause mortality			Cox proportional hazard result; relapse-related mortality		
	n	*N*	%	*n*	*N*	%	*n*	*N*	%	*n*	*N*	%	Coefficient	Risk ratio	*p*	Coefficient	Risk ratio	*p*
All patients	31	45	68.9	20	45	44.4	9	45	20	16	45	35.5	N/A	-	-	N/A	-	-
Age > 10 years	18	27	66.7	9	27	33.3	4	27	14.8	8	27	29.6	0.26	1.3	0.55	0.18	1.2	0.78
WCC > 100 × 10^9/L	13	17	76.5	8	17	47.1	4	17	23.5	7	17	41.2	-0.4	0.7	0.30	0.02	1.0	0.98
Male gender	23	32	71.9	12	32	37.5	5	32	15.6	11	38	34.8	0.7	2.1	0.14	0.6	1.8	0.45
Cortical thymocyte	18	24	62.5	12	24	50.0	8	23	34.7	7	23	30.4	-1.0	0.4	0.01	-1.1	0.30	0.05
Aberrant CD13 expression	8	16	50.0	4	16	25.0	1	16	6.3	6	16	37.5	0.9	2.5	0.04	1.1	2.9	0.13

N/A, not applicable; WCC, white cell count.
†, Median follow-up period of 37 months.

Discussion

In this study assessing the characteristics of T-ALL diagnosed in the Johannesburg state sector, T-ALL was found to comprise > 30% of both adult and paediatric ALL. This is substantially higher than the frequency of T-lineage ALL reported previously, with T-ALL comprising ~18% – 23% of ALL in adults[1,2] and 7% – 15% of childhood cases[3,4,5,6,7,8,9] in the international literature. This high frequency is comparable to that described amongst African-American patients (~25%),[12,13] and suggests a relative predisposition to T-lineage ALL amongst individuals of African descent. As reported previously, T-ALL was more common in men, with a more pronounced male predominance in adulthood (M:F = 5.3:1). The reason for the increased incidence of T-ALL (and other haematological malignancies) in men and boys is unknown, but suggested contributory factors include differences in occupational exposures (to pesticides and petrochemical products for instance), as well as subtle differences in the frequency and timing of various infectious diseases.[19]

The cortical thymocyte subtype was the most common immunophenotypic variant seen, predominating in children, whilst an even distribution of the cortical thymocyte, pre-T-cell and early T-precursor subtypes was seen in adult patients. The frequency of the cortical thymocyte subtype was generally somewhat higher than that reported in studies from other parts of the world, whilst the late T-cell immunophenotype was less common.[20,21,22,23] Aberrant myeloid antigen expression was detected in 57.7% of the patients, including 42.3% expressing aberrant CD13. This is similar to the rate of aberrant myeloid antigen expression reported in the United Kingdom (> 50.0%)[2] and Morocco (55.0%),[22] but substantially higher than that described in the United States (US) (19.0% – 32.0%[24,25]) and France (10.0%).[21] All-cause mortality rates were shown to be independently associated with the presence of a cortical thymocyte immunophenotype and aberrant CD13 expression on Cox proportional hazard analysis, with superior survival in the common thymocyte cases and poorer survival in those expressing aberrant CD13. This finding is likely to reflect the effects of integral differences in disease biology.

The genetic landscape of T-ALL in this study showed substantial differences from that reported elsewhere, with a higher frequency of karyotypic abnormalities than is typically seen (76.2% as compared to 50.0% – 70.0%). As reported elsewhere, there was high genetic heterogeneity in our setting, without a dominant genetic subgroup. The frequencies of the translocation t(10;11) (PICALM-MLLT10) and abnormalities involving the TLX1 (HOX11) and TLX3 (HOX 11L2) genes were low, but this may be because of the lack of available FISH probes for these aberrations in our centre, as they may be cytogenetically cryptic. Abnormalities of chromosome 6q were the most common derangement detected (present in 19.0% of the cases), involving the q21 region on chromosome 6 in all but one case. Chromosome 6q abnormalities affecting this region have been reported to be common in lymphoblastic leukaemia previously,[2,17,26,27] with an even higher frequency when tested for with more sensitive molecular techniques.[27] As reported in the international literature,[2,17,26] abnormalities of chromosome 6q were not prognostically relevant in this cohort. Notably, two of the patients with a 6q abnormality had a translocation t(6;12), one with breakpoints at (q?21;p?11.2) and the other at (q?23;p13). A similar translocation has been described previously in a single case of T-ALL, as well as in a small number of other haematolymphoid malignancies.[28] This was shown to involve the ETS family transcription factor (ETV6) and Fyn-related SRC family tyrosine kinase (FRK) genes at chromosomes 12p13 and 6q21 respectively in a patient with acute myeloid leukaemia, causing deregulated activation of the FRK tyrosine kinase.[29] Chromosome 6q deletions are also associated with ectopic expression of the TAL1 transcription factor, which is a common finding on transcriptional profiling of T-ALL in the developed world.[30] A transcriptome study of T-ALL with 6q deletions in SA would be of interest to further assess for a potentially common molecular drug-target in order to improve the poor survival rates in our setting.

High-risk features were highly prevalent, being present in 81.4% of cases overall and in 52.4% of children < 10 years of age. This was accompanied by very poor survival rates (in spite of the relatively short median follow-up period [37 months]), with 77.8% of patients having demised at the time of data collection (including > 70.0% of the children < 10 years and > 85.0% of the adults). These survival rates compare very poorly with those reported elsewhere, with long-term survival rates ranging from 27.0% to 52.0% in adults[2] and 60.0% – 80.0% in children in the United States and Europe.[7,8,12] High-risk features were significantly more common in patients with T-ALL versus B-ALL, and this was accompanied by significantly poorer survival rates amongst the patients with T-ALL. However, the overall crude survival rates did not differ significantly between patients with T-ALL and either high-risk or low-risk clinical features, and there was no significant difference in survival according to MRD status. Although this may be in part because of the limited sample size and the fairly insensitive nature of MRD testing in the Johannesburg state sector, the findings suggest that conventional risk factors do not satisfactorily risk-stratify patients in our setting. Given the very high mortality rates in this study, it would appear prudent to regard all T-ALL as high-risk disease in the state-sector context. Notably, although MRD status was not significantly predictive of overall survival, MRD-positivity postinduction was significantly associated with particularly short survival time (< 12 months) because of early disease relapse.

In contrast to previous reports which suggested that outcomes are superior in adults with T-ALL as compared to those with B-ALL,[1,11] the mortality rates were similarly poor amongst adult patients with B-ALL and T-ALL in this study (83.3% [B-ALL] vs 86.7% [T-ALL]). The cause of the poor survival rates is probably multifactorial in nature; relapse was the dominant cause of death, which is likely to be at least partially

attributable to highly restricted access to haemopoietic stem cell transplantation in the SA state sector. As we reported previously in the setting of B-ALL, sepsis also caused a very substantial proportion of the deaths (> 40.0%), which highlights the need for an improvement in neutropenic support in our setting.

Conclusion

This study has demonstrated the frequency of T-ALL in the SA state sector to be substantially higher than that reported in other parts of the world, with a prominence of high-risk features and differences in the cytogenetic landscape. Survival rates are very poor, both because of disease relapse and sepsis-related mortality. This highlights the need for new treatment strategies in our setting.

Acknowledgements

We 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: (1) the flow cytometry laboratory at the CMJAH; (2) the somatic cell genetics unit at the CMJAH; (3) the morphology units of the CMJAH, the Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital; (4) the medical oncology unit at the CMJAH; (5) the paediatric oncology units at the CMJAH and CHBAH; (6) the clinical haematology unit at the CHBAH; (7) the 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. T.W. and P.W. provided editorial input. K.H. performed data collection and provided editorial input.

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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