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Outcomes of an acute lymphoblastic leukaemia cohort between 2008 and 2017 at a South African paediatric oncology unit

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Background: Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer, yet few studies have reported the treatment outcomes, toxicity patterns and relapse rates in low- and middle-income countries.

Aim: To investigate overall survival (OS) and toxicity patterns in children with ALL.

Setting: The study took place at Tygerberg Hospital, South Africa.

Methods: Data on demographics, disease, treatment, toxicity and outcome data were collected over ten years. Descriptive statistics and associations were calculated. Overall survival was estimated using Kaplan–Meier curves.

Results: A total of 112 patients (male-to-female ratio 1:0.6) had a median age of 4.6 years (IQR 2.9–8.4). The 5-year OS was 65.7% (95% CI 56.0% – 74.6%), and the 5-year EFS was 64.8% (95% CI 55.0% – 73.8%). Standard-risk patients had higher 5-year OS of 74.4% (95% CI 57.9% – 87.0%) versus 60.9% (95% CI 48.4% – 72.4%) for high-risk patients. Most relapses (20.5%; $n = 23$) occurred in high-risk patients (82.6%, 19/23) ($p = 0.049$). Patients with Hyperleukocytosis (23%; $n = 26$) was linked to increased relapse risk (OR 5.0; 95% CI 1.5% – 17.5%; $p = 0.026$). Ten patients (8.9%) died while on maintenance treatment. Grade 3 and 4 haematological toxicity occurred in 18% and 19%, respectively. Delays in maintenance initiation occurred in 29% of patients, and 8% required blood product support.

Conclusion: The OS in standard-risk ALL improved to 74.4%, while overall OS was 65.7%. Hyperleukocytosis at diagnosis was associated with increased relapse risk.

Contribution: This study highlights the burden of haematological toxicity in South African children treated on a contemporary ALL regimen, with frequent treatment delays and need for blood product support.

Keywords: paediatric acute lymphoblastic leukaemia; ALL; childhood leukaemia; toxicity; relapse; survival outcomes childhood ALL.

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer in South Africa. The age-specific incidence rate (ASIR) from 1987 to 2007 was 11.9 per million children.[1] Leukaemia-specific survival rates in African populations are largely unknown, as the estimates are either not standardised or less reliable, and therefore were not reflected in the largest population-based comparison of survival of childhood leukaemia from 1995 to 2009.[2] In well-resourced settings, the management of childhood ALL has improved over the past 50 years, with cure rates approaching 90%.[3] The outcomes for children with ALL managed at Tygerberg oncology unit (POU) were last reported in 2006, with an overall survival (OS) rate of 66%.[4] A recent registry-based study showed that ALL patients had the best OS (69.6%) when reviewing trends in survival from all childhood cancers at Tygerberg Hospital from 1994 to 2014.[5] Obstacles to effective childhood cancer treatment in South Africa include limited resources, comorbid infections (such as human immunodeficiency virus [HIV]) and malnutrition.[6] To the best of our knowledge, the nature and extent of chemotherapy-related toxicity suffered by children treated for ALL have not been investigated in South Africa.

Methods

This retrospective cohort study was conducted at Tygerberg Hospital. The study included all children and adolescents younger than 16 years old with newly diagnosed ALL between

Note: Additional supporting information may be found in the online version of this article as Online Appendix 1.

January 2008 and December 2017. Data collection included demographic characteristics: age at diagnosis, sex and socioeconomic profile using household income as a proxy, coded as H-status. H0 households (formally unemployed) and all children under six years of age received free healthcare. H1 (R0–< R5800 monthly income), H2 (R5800–R20 000 monthly income) and H3 (> R20 000 monthly income) households paid healthcare costs relative to their income according to a state needs assessment.[7,8] The clinical data included: white blood cell count (WBC) at diagnosis, leukaemia immunophenotype profile, extra-medullary involvement (central nervous system [CNS] or testicular), day 7 and day 28 bone marrow (BM) biopsy results and clinical status at last follow-up (complete remission, relapse, death or lost to follow-up). The cause of death was recorded as progressive disease (refractory or relapsed disease) or toxicity-related. Treatment abandonment was defined as care termination by the caregiver and/or when more than six months had elapsed with non-attendance of a scheduled treatment visit. Patient identifying data and demographic data were anonymised by the allocation of a unique study number during the process of data collection and analysis, and a waiver of written informed consent was obtained. The Health Research Ethics Committee of Stellenbosch University provided ethics approval (HREC no: S19/07/120). Acute lymphoblastic leukaemia was diagnosed when a BM investigation showed ≥ 25% lymphoblasts, and flow cytometric analysis determined the immunophenotype. Morphological remission on day 28 was defined as < 5% lymphoblasts in the BM aspirate with normal haematopoiesis. Central nervous system involvement was classified as follows: CNS 1: < 5 WBCs/mm^3, no blasts; CNS 2: < 5 WBCs/mm^3 with blasts; CNS 3: > 5 WBCs/mm3 with blasts.[9] Bone marrow samples were tested for karyotype analysis and a limited cytogenetic panel, which included t(12;21), t(1; 19), KMT2A rearrangements and t(9;22). Testing for minimal residual disease (MRD) was not available during the study period. Patients over 10 years of age, with an initial WBC count of > 50 × 10^9/L, T-cell immunophenotype, extra-medullary infiltration or who did not achieve morphological remission on day 28, were classified as high risk (HR). Hyperleukocytosis was defined as a WBC count > 100 × 10^9/L.[10] All other patients were classified as standard risk (SR).[11] Treatment protocols were based on the Children's Oncology Group (COG) and Berlin-Frankfurt-Münster (BFM) ALL protocols. Grading of haematologic toxicity was based on the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[12] Accordingly, grade 4 toxicity was characterised by an absolute neutrophil count (ANC) <0.50 × 10^9/L, anaemia (haemoglobin (Hb) < 8 g/dl with life-threatening consequences) and thrombocytopenia <25 × 10^9/L. Grade 3 toxicity was assigned for an ANC <1.0–0.5 × 10^9/L, anaemia (Hb < 8 g/dl) and a platelet count of <50–25 × 10^9/L. Relapsed disease was diagnosed based on BM re-infiltration with ≥ 25% blasts, or blasts in extra-medullary sites. Early relapse was defined as the event occurring <18 months from diagnosis, and late relapse after >18 months.[13] Persistent (> 5%) blast infiltration on day 28 post-induction BM was classified as induction failure.

Statistical analysis

All analyses were performed using Stata Statistical Software, Release 18 (StataCorp LLC, College Station, Texas, United States). Basic descriptive statistics were calculated, including frequencies, proportions and their 95% confidence intervals (CIs) for categorical variables, as well as means, medians, standard deviations (s.d.s), and interquartile ranges (IQRs) for continuous variables. *t* tests were used to compare continuous variables where appropriate, while Chi-squared tests or Fisher's exact tests were used for categorical variables. All significant variables identified in univariate analyses were included in multivariate regression models to assess their independent associations with different outcomes. Logistic regression was used for analysis involving risk group, relapse and immunophenotype. Results were presented as odds ratios (OR) and 95% Cls. Five-year OS and event-free survival (EFS) were calculated using the Kaplan–Meier survival analysis from the date of diagnosis to the date of an event (induction failure, relapse or death) and patients without an event were censored at 5 years. Kaplan–Meier survival curves were generated and compared using log-rank tests. Induction mortality rate was calculated as the number of deaths during induction divided by the total number of children starting induction, multiplied by 100%. Univariate Cox proportional hazards regression analyses were performed to identify risk factors associated with survival or the occurrence of an event. The identified risk factors were entered into a multivariable Cox regression model, and the hazard ratios with their 95% CIs were calculated. *p*-values ≤ 0.05 was considered statistically significant.

Ethical considerations

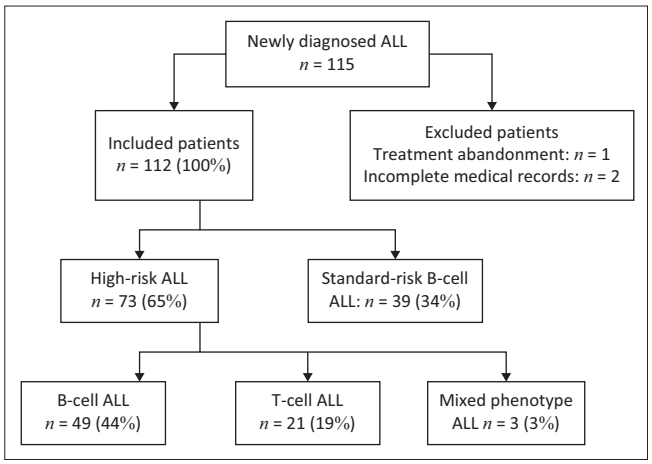
Ethical clearance to conduct this study was obtained from Stellenbosch University Health Research Ethics Committee (No. S19/07/120).

Results

A total of115 children were diagnosed with ALL from 2008 to 2017 at Tygerberg Hospital (Figure 1). Three children were excluded as one had abandoned treatment and two had incomplete medical records. Four infants were included in the initial data analysis. However, their survival outcomes were excluded from the statistical analysis because of unique disease biology, genetic alterations, risk stratification and treatment protocols.[14]

Most patients were males (62.5%; *n* = 70) (male-to-female ratio 1:0.6). The median age was 4.6 years (IQR 2.9–8.4 years). Most households (57%, *n* = 65) earned a low income of less than R5800 (USD 318) per month. Of note, patients with a T-cell immunophenotype had a low socioeconomic status of H0 or H1 in 57% (*n* = 12) and H2 or H3 in 43% (*n* = 9) of patients (Table 1). B-cell ALL (78%, *n* = 88) was the most common subtype. Just over half (56%; 49/88) were classified as HR versus 44% (39/88) as SR. Nearly a fifth of patients had T-cell ALL (19%, *n* = 21), and three patients (3%) were diagnosed with mixed phenotype leukaemia (MPAL), all

managed as HR (Figure 1). Most (69.9%, 51/73) of those with HR disease were male ($p = 0.028$). Fifteen patients (13%) had extra-medullary ALL at diagnosis: twelve (10%) had CNS, and three (3%) had testicular involvement. Half of patients (51%; $n = 57$) had a WBC of below 20×10^9/L at diagnosis (mean 94.3×10^9/L; SD 167.8×10^9/L), while 26 patients (23%) presented with hyperleukocytosis. Four variables were significantly associated with HR disease in the univariate analysis: age ($p = 0.045$), sex ($p = 0.028$), absolute WBC ($p < 0.001$) and relapse ($p = 0.049$). Only absolute WBC ($p = 0.004$) and age at diagnosis ($p = 0.007$) remained statistically significant in the multivariate analysis after adjusting for other factors (Table 1).



ALL, acute lymphoblastic leukaemia.

FIGURE 1: Study population according to acute lymphoblastic leukaemia subtypes.

Cytogenetic analysis was performed in 50 (45%) patients. The majority had favourable cytogenetics, namely *t*(12;21) detected in 32% ($n = 16$) and hyperdiploidy in 14% ($n = 7$). Other cytogenetic results included *t*(1;19) (2%; 1/50), *t*(9;22) (8%; 4/50) and KMT2A rearrangement (16%; 8/50). A complex karyotype or a cytogenetic result not included in the panel comprised 28% (14/50) of cytogenetic results. Cytogenetics were performed for four patients with induction failure. Two patients with induction failure had KMT2A gene rearrangements, one patient had a *t*(9;22) translocation, and one had tetrasomy of chromosome 5 detected at diagnosis. T-cell ALL was significantly more prevalent among older children, particularly those aged 10–14 years ($p = 0.014$). The median age at diagnosis for this group was 8.3 years (IQR 4.6–10.8), which is notably higher than that for B-cell ALL at 4.3 years (IQR 2.5–7.4) ($p = 0.002$). A strong male predominance was observed, with T-cell ALL occurring six times more frequently in boys (86%, 18/21) than in girls (14%, 3/21) ($p = 0.036$). T-cell ALL cases also

TABLE 1: Demographic and disease information categorised by risk group.

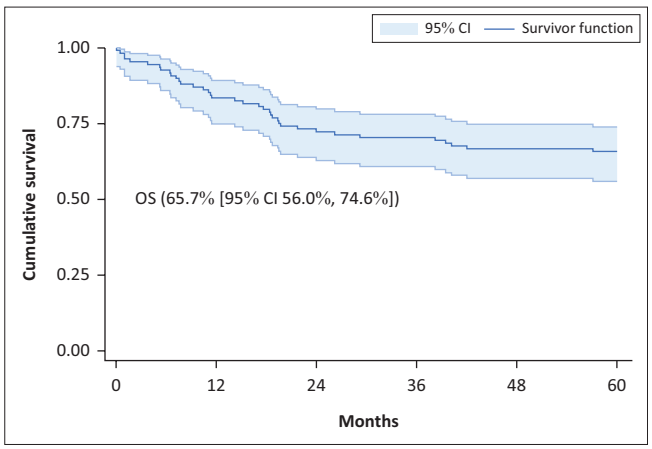
Demographic and laboratory characteristics	Whole cohort				Standard risk				High risk				*p*-value	Multivariate		
	N	%	Median	IQR	*n*	%	Median	IQR	*n*	%	Median	IQR		OR	95% CI	*p*-value
Number (*n*)	112.0	-	-	-	73	-	-	-	39	-	-	-	-	-	-	-
Age																
Age at diagnosis (years)	-	-	4.6	2.9–8.4	-	-	3.8	2.8–6.2	-	-	5.5	2.9–9.7	0.045	1.20	1.1–1.4	0.008
0–4	-	-	-	-	26	45	-	-	32	55	-	-	0.018	-	-	-
5–9	-	-	-	-	11	32	-	-	23	68	-	-	-	2.10	0.8–5.8	0.133
10–14	-	-	-	-	2	10	-	-	18	90	-	-	-	9.1 0	1.7–48.9	0.010
Sex																
Male	70.0	62	-	-	19	27	-	-	51	73	-	-	0.028	2.4 0	0.9–6.3	0.071
Female	42.0	38	-	-	20	48	-	-	22	52	-	-	-	-	-	-
Socioeconomic classification (H-code)	-	-	-	-	-	-	-	-	-	-	-	-	0.108	-	-	-
H0 (no income)	30.0	26	-	-	5	17	-	-	25	83	-	-	-	-	-	-
H1 (R0–R5800/month)	35.0	31	-	-	14	40	-	-	21	60	-	-	-	-	-	-
H2 (R5800–R20 000/month)	15.0	13	-	-	6	40	-	-	9	60	-	-	-	-	-	-
H3 (> R20 000/month)	32.0	30	-	-	14	44	-	-	18	56	-	-	-	-	-	-
Median (IQR) WBC at presentation	94.3	-	-	-	-	-	11.6	5.5–23.0	-	-	44.0	11–211	< 0.001	1.03	1.01–1.1	0.003
≤ 20×10^9/L	57.0	51	-	-	29	51	-	-	28	49	-	-	< 0.001	2.30	0.8–6.4	0.100
> 20–< 100×10^9/L	29.0	26	-	-	10	34	-	-	19	66	-	-	-	-	-	-
≥ 100×10^9/L	26.0	23	-	-	-		-	-	26	100	-	-	-	-	-	-
Immunophenotype	-	-	-	-			-	-	-	-	-	-	< 0.001	-	-	-
B-cell ALL	88.0	78	-	-	39	44	-	-	49	56	-	-	-	-	-	-
T-cell ALL	21.0	19	-	-	-	-	-	-	21	100	-	-	-	-	-	-
MPAL	3.0	3	-	-	-	-	-	-	3	100	-	-	-	-	-	-
CNS status at diagnosis	-	-	-	-	-	-	-	-	-	-	-	-	0.009	-	-	-
CNS 1	98.0	87	-	-	39	40	-	-	59	60	-	-	-	-	-	-
CNS 2	1.0	1	-	-	-	-	-	-	1	100	-	-	-	-	-	-
CNS 3	12.0	11	-	-	-	-	-	-	12	100	-	-	-	-	-	-
Bloody tap	1.0	1	-	-	-	-	-	-	1	100	-	-	-	-	-	-

ALL, acute lymphoblastic leukaemia; CNS, central nervous system; IQR, interquartile range; MPAL, mixed phenotype acute leukaemia; WBC, white blood cell count; CI, confidence interval; OR, odds ratio.

presented with significantly higher WBCs at diagnosis, with a median WBC of 141.8 × 10^9/L (IQR 19.3–352.0), compared to 13.6 × 10^9/L (IQR 7.0–57.4) in B-cell ALL cases (p = 0.018). Central nervous system3 involvement at diagnosis was identified in 19.1% (4/21) of T-cell ALL patients (Online Appendix 1 - Table 1). Few patients (12.5%, n = 14) had a comorbid condition at the time of ALL diagnosis. Three patients were previously diagnosed with autism, and two patients suffered a stroke prior to ALL diagnosis. Other comorbidities included one of each with the following diagnoses: attention-deficit hyperactivity disorder, HIV infection, obesity, meningitis, mesenteric adenitis, tuberculosis, juvenile idiopathic arthritis, cerebral palsy and Down syndrome. The majority (72%, n = 81) of patients received treatment according to a modified COG protocol, and 24% (n = 27) received treatment according to a modified BFM-ALL protocol. Four infants were treated according to the Interfant99 protocol. Most patients (88%, n = 99) achieved morphological remission at the end of induction. Thirteen patients (12%) with HR disease did not achieve remission post-induction. Of these, six (46.2%) presented with hyperleukocytosis, 11 (85%) were males, 10 (77%) had B-cell ALL, and three (23%) had T-cell ALL. Eleven of the 13 patients who failed remission induction were treated according to the modified COG protocol, one patient according to the BFM-ALL protocol, and one was managed according to the Interfant99 protocol. Four (31%, 4/13) later relapsed, compared to 19% (19/99) of those with induction remission who relapsed later (p = 0.331). The 5-year OS rate for the entire cohort was 65.7% (95% CI: 56.0–74.6%) (Figure 2). Standard-risk patients had an improved 5-year OS of 74.4% (95% CI: 57.9–87.0%) versus 60.9% (95% CI: 48.4–72.4%) for high-risk patients (Figure 3). Socioeconomic classification (p = 0.047), hyperleukocytosis (p = 0.016) and relapse (p < 0.001) were significantly associated with OS (Table 2). In the Cox-regression analysis, only relapse remained significantly associated with 5-year OS, with relapsed patients having a sevenfold higher hazard of death compared to those without relapse (Hazard ratio [HR] 7.1; 95% CI: 3.3–15.1; p < 0.001) (Table 2). The cohort's 5-year EFS rate was 64.8% (95% CI: 55.0–73.8%).

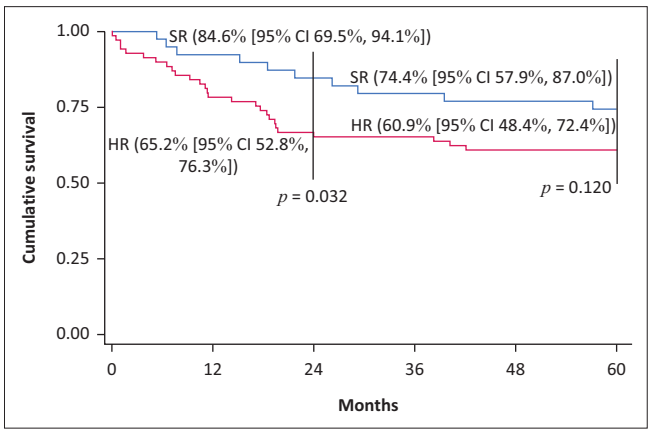
Relapses occurred in 23 patients (20.5%). Sixty-nine per cent (16/23) of all relapses occurred amongst patients with B-cell ALL, while 22% (5/23) of patients with T-cell ALL, and two patients (9%) with MPAL relapsed. Of those who relapsed, most had HR disease (82.6%; 19/23) (p = 0.049), and 12 patients (52%) had hyperleukocytosis at diagnosis (p = 0.001). Logistic regression analysis showed that patients with hyperleukocytosis had a significantly increased risk of relapse compared to those with normal WBC counts (OR 5.0; 95% CI 1.5–17.5) (p = 0.026), while HR classification was no longer significant (OR 1.5; 95% CI 0.4–5.7) (p = 0.538) (Online Appendix 1 Table 2). The relapse rate was not significantly different for age (p = 0.811), sex (p = 0.432), socioeconomic classification (p = 0.083) and induction response (p = 0.331) (Online Appendix 1 Table 2). Twenty patients (19%) suffered isolated bone marrow recurrences, one patient (0.9%) experienced an isolated CNS relapse (CNS 1 status at diagnosis), and two patients (1.8%) experienced a mixed relapse (one patient had CNS3 status at diagnosis and one patient had CNS 2 status at diagnosis). Of the 36 deaths (32%), 28 (78%) occurred in the HR group, and eight (22%) occurred amongst SR patients. Most deaths occurred within the first two years after diagnosis, and the survival difference between the SR and HR groups was statistically significant (p = 0.032) (Figure 3). However, beyond this period, the 5-year survival difference was no longer statistically significant (p = 0.120) (Figure 3).

The same proportions of patients treated according to the modified COG protocol (29%; 24/81) and the BFM-ALL protocol (29%; 8/27) died. Causes of death were progression of disease (refractory or relapse disease) in 16 patients (44%) and toxicity-related causes (neutropenic sepsis) in 20 patients (55%). The induction mortality rate was 3.5% for this cohort (n = 4). One patient was HIV positive and developed an axonal variant of Guillain-Barré syndrome. One patient with T-cell ALL and hyperleukocytosis died two days after the start of induction therapy because of progressive disease. Eight patients (7%) died during the delayed intensification therapy phase because of sepsis. Ten patients (8.9%) died while on maintenance treatment. Of these, four died because of relapse and progressive disease (and were regarded as palliative cases), and six died due to



ALL, acute lymphoblastic leukaemia; CI, confidence interval; OS, overall survival.

FIGURE 2: Acute lymphoblastic leukaemia 5-year overall survival for the whole cohort.



ALL, acute lymphoblastic leukaemia; CI, confidence interval; HR, high risk; SR, standard risk.

FIGURE 3: Acute lymphoblastic leukaemia 5-year overall survival according to risk group and deaths occurring at 2 years after diagnosis versus deaths at 5 years after diagnosis.

TABLE 2: Factors associated with 5-year overall survival.

Demographic and laboratory characteristics	Whole cohort		Univariate			Multivariate		
	5-year OS	95% CI	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age (years)								
0–4	69.1	55.2–80.9	-	-	-	-	-	-
5–9	69.7	51.3–84.4	1.1	0.5–2.5	0.812	-	-	-
10–14	50.0	27.2–72.8	2.1	0.95–4.7	0.066	-	-	-
Sex								
Male	65.7	56.0–74.6	-	-	-	-	-	-
Female	65.9	49.4–79.9	1.1	0.8–2.1	0.815	-	-	-
Socioeconomic classification								
H0 & H1 (< R5800)	57.1	44.0–69.5	-	-	-	-	-	-
H2 & H3 (> R5800)	77.8	62.9–88.8	0.5	0.2–1	0.053	-	-	-
WBC								
≤ 20 x10^9/L	71.9	58.5–83.0	1.1	0.4–2.6	0.906	0.9	0.4–2.2	0.843
> 20 ×10^9/L- < 100 x10^9/L	75.0	55.1–89.3	-	-	-	-	-	-
≥ 100 × 10^9/L	39.1	19.7–61.5	2.8	1.1–7.1	0.032	1.4	0.5–4.0	0.534
Risk group								
Standard risk	74.4	57.9–87.0	-	-	-	-	-	-
High risk	60.9	48.4–72.4	1.6	0.8–3.4	0.187	-	-	-
Immunophenotype								
B-cell ALL	67.9	56.8–77.6	-	-	-	-	-	-
T-cell ALL	66.7	43.0–85.4	1.0	0.4–2.3	0.923	0.7	0.2–1.8	0.410
MPAL	0	0.0–0.7	6.3	1.9–21.4	0.003	1.5	0.4–5.5	0.530
Relapse								
No relapse	5.0	0.1–24.9	-	-	-	-	-	-
Relapsed	79.5	69.6–87.4	8.2	4.1–16.5	< 0.001	7.1	3.3–15.2	< 0.001
Induction response								
Complete remission	67.7	57.4–76.9	-	-	-	-	-	-
Induction failure	50.0	21.1–78.9	0.6	0.2–1.5	0.258	-	-	-

ALL, acute lymphoblastic leukaemia; CI, confidence interval; MPAL, mixed phenotype acute leukaemia; OS, overall survival; WBC, white blood cell count.

sepsis. Most patients who died during maintenance were males ($n = 8$) with a T-cell immunophenotype ($n = 9$) and were receiving high-risk maintenance therapy ($n = 5$). The prevalence rate of haematotoxicity during maintenance therapy was 48% (54 episodes) for the whole cohort. Within the first six months of starting maintenance therapy, grade 3 haematological toxicity was experienced by 20 patients (18%) and grade 4 toxicity by 21 patients (19%). Haematological toxicity was experienced less frequently during the later phases of maintenance therapy (beyond six months on therapy): grade 3 ($n = 7$) and grade 4 ($n = 6$). Most of those who experienced haematological toxicity were treated on a COG-based ALL maintenance regimen (92% of recorded episodes). Of those who died during maintenance therapy ($n = 10$), half experienced haematological toxicity: grade 3 ($n = 1$) and grade 4 ($n = 4$). Thirty-two patients (29%) experienced a delay in initiating any maintenance phase of therapy, and nine (8%) required a blood product transfusion during maintenance therapy. One patient who died during cycle four of maintenance therapy had a normal absolute neutrophil count at the last clinic visit. This patient died soon after presentation to a local health facility, and the circumstances surrounding the death are unclear. One patient who died of sepsis had a genetic mutation (C677T) on the methylenetetrahydrofolate reductase (MTHFR) gene detected.

Discussion

The 5-year OS for this ALL cohort (65.7%) is similar to previously reported data from our centre (66%) in 2006 (4), with SR ALL patients achieving improved outcomes (74.4%). The outcomes for HR disease (5-year OS 61%) are similar to those reported in Egypt (58.1%), Pakistan (64.9%) and Brazil (59%).[15,16,17] Hyperleukocytosis at presentation was the only adverse prognostic factor independently associated with relapse. Wessels et al. previously reported age and WBC at diagnosis as poor prognostic factors for patients with ALL treated at Tygerberg Hospital.[18] The outcome of childhood ALL in low- and middle-income countries (LMICs) is lagging in many aspects, including diagnosis, risk stratification, access to treatment and supportive care.[19] The Tygerberg paediatric oncology unit has reliable access to immunophenotyping by flow cytometry, which has classified the majority of cases as B-cell ALL (78%) and nearly a fifth as T-cell ALL (19%). T-cell ALL is characterised by a two to three times higher incidence in boys, a higher proportion of patients with African ancestry, high initial WBC counts and higher frequencies of mediastinal mass and CNS involvement.[20] In our cohort, this male predominance was even more pronounced, with a male-to-female ratio of 6:1. The incidence of T-cell ALL in this cohort is higher than that reported in high-income settings (10% – 15%), and compared to Brazilian (10.5%) and Pakistani (11%) cohorts, but slightly lower than an Egyptian cohort (22%) described by Abdelmabood et al.[15] Previous international studies suggested that T-phenotypes were associated with an unfavourable socioeconomic status,[21] and in our cohort, the majority of those with T-cell immunophenotype were classified in the lower

income brackets. T-cell immunophenotype is considered an adverse clinical prognostic factor in childhood ALL with an increased risk of induction failure, early relapse and isolated CNS relapses.[22] Overall, the genetic basis of T-cell ALL predisposition remains poorly understood.[20,23] Cytogenetic studies assisted with risk stratification in half of the cohort, as the local haematopathology laboratory adopted a standard ALL cytogenetic panel policy only after this study period. Cytogenetic testing in our cohort showed that the majority had favourable markers such as *t*(12;21) and hyperdiploidy detected. This is associated with younger age at diagnosis (3–6 years), high sensitivity to chemotherapy and low relapse rates.[24] A study conducted in Johannesburg, South Africa, showed that *t*(1;19) was the most common recurrent genetic abnormality detected among patients with B-cell ALL (23.7%), while it was only detected in 2% of patients tested in our cohort.[25] In the future, expanded cytogenetic testing will help characterise cytogenetic aberrations in children presenting to our unit, as international studies suggest that the frequency of genetic abnormalities in childhood leukaemia varies by ethnicity and geographic region.[26,27]

In LMICs, such as Mexico and Brazil, high induction mortality rates (17% – 26%) are a major reason for poor outcomes.[28] Death during induction therapy occurred in 3.5% of children in our study. This is higher than a cohort reported in Brazil (2.6%), but lower than a reported cohort from Mexico (12%).[17,28] The leading cause of induction mortality in our cohort was neutropenic sepsis, and this may reflect numerous potential contributing factors, such as late presentation to the local hospital, a lack of healthcare staff at local clinics (and thus delayed medical intervention or a lack of realisation of the urgency of referral), a lack of transport to the local facility or lack of insight by caregivers as to the severity of symptoms. Death during maintenance therapy occurred in 10 patients (8.9%) in our cohort, compared to 13.0% – 14.6% in cohorts from Egypt and Pakistan, respectively.[15,16] The maintenance phase of ALL therapy is the longest stage of treatment (2.5 years). Haematotoxicity is a vital issue to consider as it is the main reason for treatment discontinuation or delay, leading to relapse.[29] This study showed a high rate of haematological toxicity during maintenance therapy, similar to a recently reported cohort in Ethiopia.[29] Methotrexate and 6-mercaptopurine, used in the maintenance phase, have potentially serious toxicities, including myelosuppression, which may be life-threatening and have gastrointestinal toxicity.[30] For both medicines, pharmacogenomic factors have been identified that can explain a significant portion of the variance in toxicity between patients and may serve as effective predictors of toxicity during the maintenance phase.[30] One patient who developed grade 3 haematological toxicity and died of sepsis whilst on maintenance therapy had a genetic mutation on the MTHFR gene (C677T), but this pharmacogenomic monitoring is not widely available in our setting. While haematotoxicity is well-studied in developed countries, research into its incidence and predictors in LMICs such as South Africa is still needed to guide effective patient management and improve outcomes. Every organ can be affected by acute side effects of anti-leukaemic chemotherapy, the most common being opportunistic infections, mucositis, central or peripheral neuropathy and bone marrow toxicity.[31] Measures to reduce morbidity and mortality should focus on increased patient and caregiver education on the early warning signs of sepsis and improved early transfer of patients to the paediatric oncology unit. The use of prophylactic antibiotics, apart from cotrimoxazole, is not a routine practice in our unit. Prophylactic antibiotics may help to decrease infection-related mortalities, especially in settings with high rates of malnutrition, limited access to broad-spectrum antibiotics or limited intensive care facilities.[32] Yeh et al. reported that children undergoing induction chemotherapy who received prophylactic oral ciprofloxacin and either voriconazole or micafungin during neutropenic periods had fewer episodes of bloodstream infections, no invasive fungal disease and resulted in no infection-related deaths.[32] More significantly, this prophylactic antibiotic regimen reduced episodes of febrile neutropenia, as well as the length of stay in the intensive care unit. Furthermore, therapy costs were significantly lower when utilising prophylactic antibiotics or antifungals compared to infection treatment costs.[32] However, the cost-effectiveness of using broad-spectrum antibiotics as prophylactic therapy needs further investigation in LMIC settings.

Conclusion

This retrospective study demonstrated an improved 5-year OS for SR ALL, but the cohort's overall survival is similar to that of a previously reported cohort managed in this unit. Hyperleukocytosis at diagnosis was independently associated with relapse, which in turn was strongly linked to inferior 5-year OS. We observed a higher rate of T-cell immunophenotype compared to high-income settings and other LMIC cohorts, and this may have influenced our 5-year OS negatively. Measures to improve supportive care must be prioritised as neutropenic sepsis was a major cause of death in all phases of therapy. This study reports on the burden of haematological toxicity experienced by South African children managed on contemporary ALL maintenance regimens, showing high rates of delayed initiation of maintenance courses and the need for blood product transfusions. Comprehensive cytogenetic testing at diagnosis, combined with the use of minimal residual disease measurement, can be employed to enhance risk stratification and reduce the intensity of treatment where applicable and further intensify treatment for those with very high-risk disease.

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Competing interests

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

CRediT authorship contribution

Leilah Schoonraad: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; and Writing – original draft. Anel van Zyl: Conceptualisation; Formal analysis; Methodology; Supervision; and Writing – review & editing. Sandile Ndlovu: Formal analysis; Methodology; and Writing – review & editing. Mariana Kruger: Conceptualisation; Formal analysis; Methodology; Supervision; and Writing – review & editing. All authors reviewed the article, contributed to the discussion of results, approved the final version for submission and publication and take responsibility for the integrity of its findings.

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