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RESEARCH ARTICLE

# The outcome of acute lymphoblastic leukemia in infants at National Cancer Institute Egypt: 10 years' experience

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## ABSTRACT

**Background**: Acute lymphoblastic leukemia (ALL) in infants is known to be biologically different from ALL in older children. **Aim:** We aimed to determine the clinical and laboratory characteristics, outcomes, and toxicities of infants with ALL treated with interfant-99 and St. Jude Total Therapy XV protocols at the National Cancer Institute (NCI), Egypt. **Methods:** This retrospective study included infants diagnosed with ALL between January 2010 and December 2019. **Results:** Of the total 40 cases, 25 (62.5%) were males, and 15 (37.5%) were females. Age at examination was < six months in 14 (35%) and ≥ six months in 26 (65%) cases. The total leukocyte count (TLC) at examination was >250 $x10^3$ in 11 (27.5%) cases. KMT2A rearrangement was done for 24 (60%) patients; it was wild-type in 5 (20%) and rearranged in 19 (80%) cases. 24 (60%) patients received Interfant-99, 14 (35%) received St. Jude total XV therapy, and 2 (5%) died on day 1. Relapse occurred in 10 (25%) patients. There was no difference in overall survival (OS) or event-free survival (EFS) between those treated with Interfant-99 versus St. Jude total XV therapy. The three-year OS was 26.3% for the whole group, and the three-year EFS was 14%. **Conclusions:** The patients had lower survival rates than those in the comparable studies in developed countries but are comparable to those in developing countries. Infection and sepsis, the leading causes of death, account for 78% of deaths, highlighting the importance of supportive care for such vulnerable patients.

**Keywords**: ALL, Infants, outcome, KMT2A, interfant-99

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## INTRODUCTION

Acute lymphoblastic leukemia (ALL) in infants (up to one year of age) differs biologically from ALL in older children. Infants with ALL are more often associated with a higher tumor load at diagnosis, a rearrangement in the mixed-lineage leukemia (MLL) gene, now known as KMT2A gene, and a very immature B-cell phenotype (pro-B ALL) without CD10 expression (Kang et al.,2012). Outcomes for subgroups of infants with ALL vary with the status of the KMT2A gene expression, age at diagnosis, total leukocyte count (TLC) at presentation, central nervous system (CNS) involvement, and early response to prednisone. However, these variables are interdependent, and their relative significance remains unknown (Kang et al.,2012 & Pieters et al.,2007).

In the 1980s, event free survival (EFS) was only 20–30% but improved somewhat subsequently with the development of intensified, infant-specific therapy (Reaman et al.,1985 & Lauer et al.,1998). In the Interfant-99 trial, the largest infant ALL trial conducted to date and which used an intensive 24-month regimen, the 4-year EFS was 47% (Pieters et al.,2007, Hilden et al.,2006 & Kosata et al.,2004,). While published data regarding infants with ALL is scarce in low- and middle-income countries (LMICs), that could be attributed to the already low incidence of the disease and limited medical research resources in such countries. So, we aimed to evaluate the frequency, clinical and epidemiologic features, outcome, and toxicities of infants with ALL in national cancer institute (NCI), Egypt, as well as the outcome of patients

treated on the Interfant-99 compared to the St. Jude Total Therapy XV chemotherapy protocol.

## PATIENTS AND METHODS

### Subjects

We retrospectively included 40 infants younger than or equal to 356 old days diagnosed with ALL at the NCI, Cairo University, Egypt, between January 2010 and December 2019. Patients' demographic, clinical, laboratory, and treatment characteristics were evaluated retrospectively. Two patients died on day 1 of induction; 24 received Interfant-99, and 14 received St. Jude Total Therapy XV. Chemotherapy was administered for two years; per Interfant-99, the response to prednisone is classified as good or poor based on the steroid response on day 7. If the leukemic blast cell count per microliter of blood is less than 1,000, the response to prednisone is classified as good; otherwise, it is classified as poor (Pieters et al.,2007). At the end of induction, complete remission (CR) was defined as bone marrow with less than 5% leukemic cells, regenerating hematopoiesis, and no evidence of leukemia elsewhere (Pieters et al.,2007). Patients enrolled in St. Jude Total Therapy XV, were assigned to the intermediate-risk (IR) or high-risk (HR) treatment arm based on the level of minimal residual disease (MRD) as measured by flow cytometry at the end of induction (Pui et al., 2009). All patients with KMT2A rearrangement were eligible for the interfant-99 protocol, with the exception of two patients who received St. Jude Total Therapy XV because the KMT2A rearrangement result was delayed and the patients began treatment promptly due to high TLC. CNS status was defined as CNSI (cerebrospinal fluid (CSF) with no blasts and red blood cells (RBCS) less than 10), CNS II (<5 white blood cells (WBCS)/L of CSF with blasts), and CNS III (≥5 WBCS/L of CSF with blasts or cranial nerve palsy or intracranial leukemic infiltration). Toxicities were evaluated based on version 5 of the National Cancer Institute's Common Toxicity Criteria. Patients who have been treated outside the NCI were not eligible for the study.

### Statistical Analysis

Statistical analysis was conducted using Statistical Package for the Social Sciences, version 28.0 (SPSS Inc., Chicago, IL, United States). Numbers and percentages were reported for categorical variables. The Kaplan–Meier method was used to estimate the OS and EFS rates, and the Log-Rank test was used to make comparisons. The unadjusted and adjusted hazard ratios (HR) for the outcomes of interest were calculated using the Cox proportional hazard regression model and presented as HR with their 95% confidence intervals (CI). A two-tailed p-value of less than 0.05 was considered statistically significant.

## RESULTS

Forty patients younger than 12 months were eligible for inclusion in this study. The duration of illness prior to presentation ranged from 7 to 30 days, with a median of 14 days. Twenty-four (60%) of 40 patients underwent KMT2A rearrangement testing by fluorescence in situ hybridization (FISH). It was the wild type in five (20%) cases and rearranged in 19 (80%) patients. Regarding CNS status, it was CNSI in 21 (58.3%) cases, CNSII in 2 (5.6%) cases, and CNS III in 13 (36.1%) cases (one case was considered CNS positive owing to intracranial hemorrhage); in 4 (10%) cases, it was not performed as all of them died before D7 steroid, which is the time for initial intrathecal and initial CSF sampling. The baseline characteristics and treatment details of the study participants are shown in Table 1.

At our institution, infants with ALL and wild-type KMT2A are treated by the St. Jude Total Therapy XV, whereas infants with rearranged KMT2A are treated using the Interfant-99 protocol, with the exception of two patients who received St. Jude Total Therapy XV because the KMT2A rearrangement result was delayed and the patients started treatment immediately due to high WBCs. The Interfant-99 protocol is a hybrid regimen incorporating the standard ALL treatment with acute myeloid leukemia-treating components. Fourteen patients were administered the St. Jude Total Therapy XV regimen, and 24 were given Interfant-99. The St. Jude Total Therapy XV enhanced the MRD response with a significant p-value of 0.047, but the sample size was small. Characteristics of study participants, complications and treatment outcome according to treatment protocol are

shown in Table 2. There was no significant difference in the overall survival (OS) and event free survival (EFS) between those who received the Interfant-99 protocol versus those who received St. Jude Total Therapy XV, 33.3% versus 28.6% with a P value of 0.98 and 12.5% versus 21.4% with a P value of 0.627, respectively. In terms of infectious toxicity during the induction phase, bacterial and fungal infections were comparable between the two protocols, with a p-value of 0.450. Ten (41.7%) of the interfant-99 patients developed febrile neutropenia without a documented causative organism, whereas only three (21.4%) of the St. Jude Total Therapy XV patients did so. Despite knowing that the p-value was not statistically significant, this reflects the intensity of the Interfant-99 protocol. Infectious toxicities following the induction phase did not differ between the two regimens (p=0.278). Regarding noninfectious toxicities, gastrointestinal tract (GIT) toxicity during induction was greater in the interfant-99 protocol, with five cases (20.8%) compared to one (7.1%) in the St. Jude Total Therapy XV, while other toxicities were comparable. We found that patients with rearranged KMT2A presented with unfavorable prognostic factors as shown in Table 3. they presented at a significantly younger age (less than six months), high TLC (greater than 250 x $10^3$ /$mm^3$), and a higher stage of CNS with a p-value of 0.076, 0.064, and 0.145, respectively. There was no significant difference in the OS or EFS probability between patients with different treatment protocol, KMT2A rearrangement, age group, and TLC group. The hazard ratio (HR) of mortality or event occurrence in patients with CNS III was significantly higher than patients with CNS I as shown in Table 4.

For the whole cohort, 3-year OS was 26.3% with a mean survival time of 582 (286–878) days, and 3-year EFS was 14% with a mean EFS time of 333 (123–544) days, as shown in (Figure 1). Regarding disease relapse, ten (25%) patients experienced a relapse in this study. Relapses occurred in the bone marrow (BM) in four (40%) of ten patients, in the CNS in three (30%), and the BM and CNS in three (30%). Of all, 30% of relapsed cases died. Regarding the infectious toxicities of the study participants, bacterial infection occurred in 24 patients, with gram-negative, multidrug-resistant (MDR) bacteria being the most common cause. Gram-negative MDR bacteria were detected in 11 patients (27.5% during the induction phase) and two patients (after the induction phase). Non-infectious toxicities were observed in 19 patients; five patients developed GIT toxicity, including grade 3 typhlitis in three patients and grade 3 diarrhea in two patients. Five patients developed hepatotoxicity with grade 3–4 hyperbilirubinemia. Four patients exhibited cardiotoxicity consistent with grade II–III left ventricular dysfunction. Two patients corresponding to the CNS III group and one patient corresponding to the CNS I group exhibited neurotoxicity. In two patients, neurotoxicity manifested as grade 3–4 convulsions, and in one patient, it manifested as a disturbance in the level of consciousness. Respiratory failure developed in two patients with grades 3–4, as shown in (Table 5). Eighteen (64.3%) patients died during induction before remission assessment, and six (21.4%) patients died in CR. The causes of death for six patients who died in CR were septic shock and multiple organ failure in four cases, hepatotoxicity and liver cell failure in one case, and hemorrhage and hypovolemic shock in the other. Four (14.3%) patients died of the disease as shown in (Figure 2). Infection and sepsis were the leading causes of mortality among study participants in 22 cases (78%).

## DISCUSSION

ALL in infants is a rare disease that accounts for approximately 2.5% to 5% of childhood ALL (Biondi et al.,2000). Infant leukemia is still associated with poor outcomes despite the improved prognosis for childhood leukemia (Pui et al.,1996 & Chessells et al., 2002). In infants, the clinical and biological characteristics of ALL are frequently different from those of older children (Silverman, 2007 & Hilden et al.,2006). Very little is known regarding the clinical and biological characteristics of infantile ALL, particularly in LMICs. In this study, one of our objectives is to determine whether standard ALL treatment, like St. Jude Total Therapy XV, is preferred to infant-specific intensified therapy, such as interfant-99.

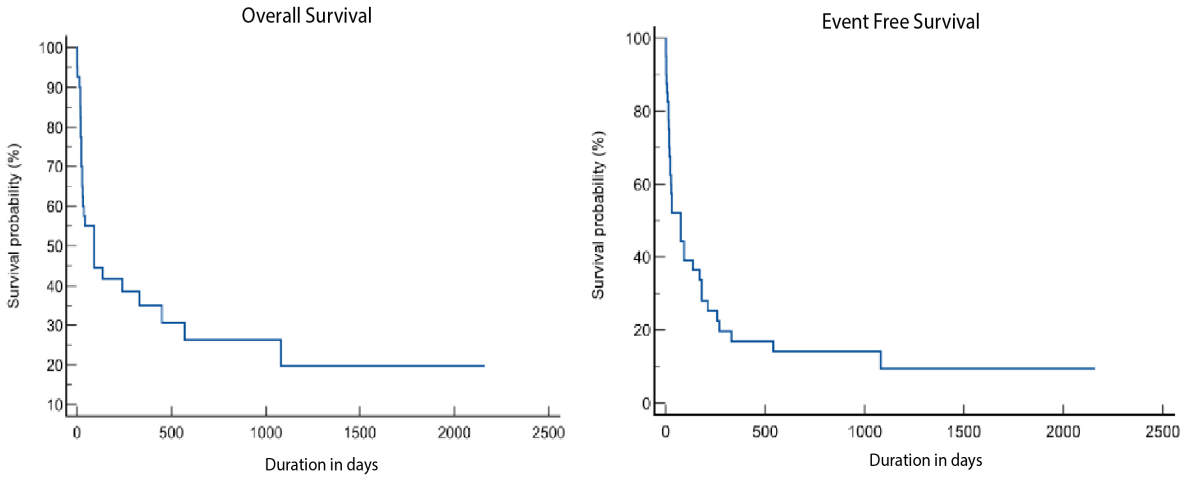


**Figure 1.** A:3-year overall survival in the study participants. B: 3-year EFS free survival in the study participants.

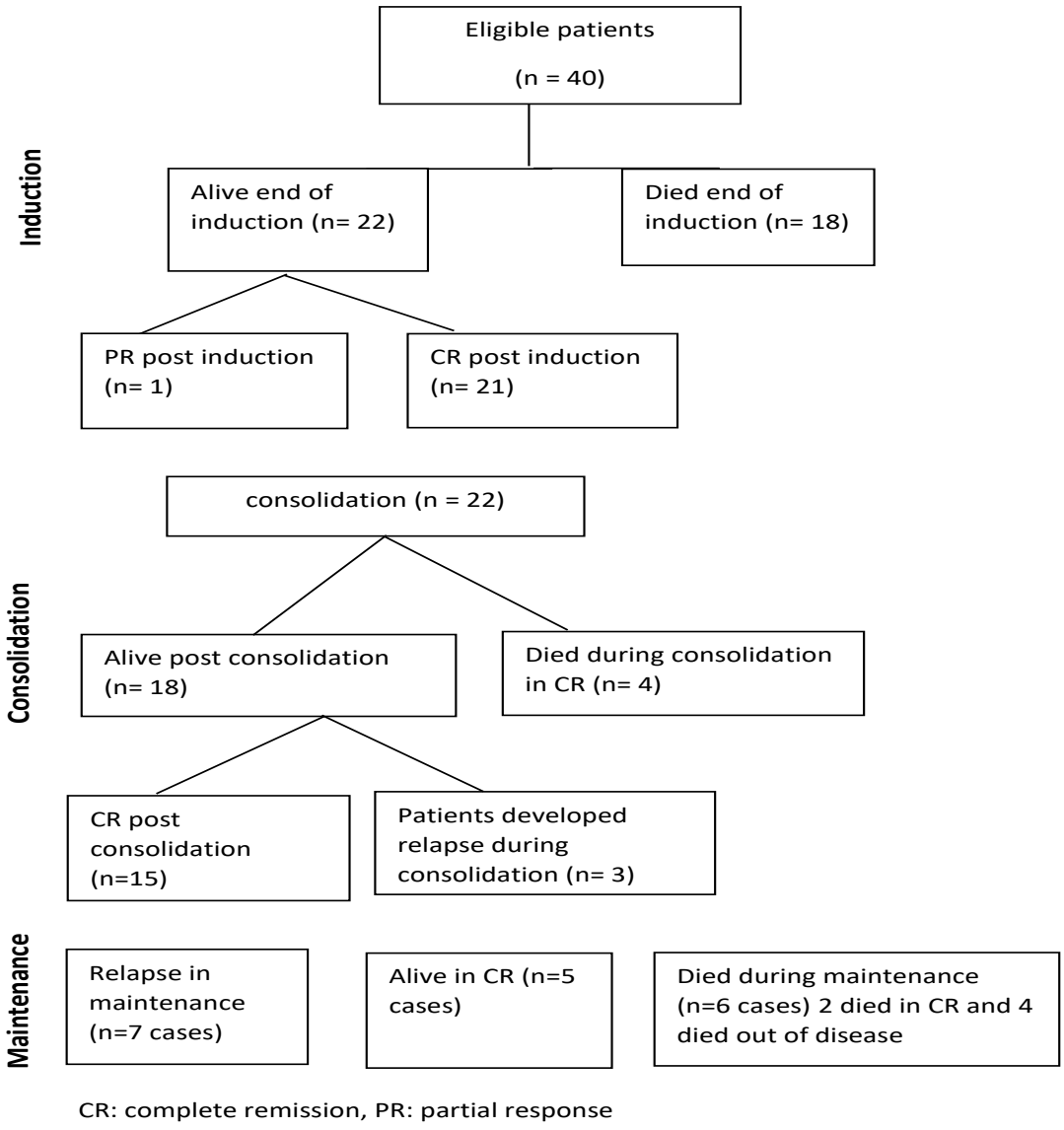


**Figure 2.** Flow chart for the studied patients

**Table 1.** Characteristics of the study participants at diagnosis.

| | | Study participants (n=40) |
|---|---|---|
| Gender | Male | 25 (62.5%) |
| | Female | 15 (37.5%) |
| Age at diagnosis (months) | < 6 months | 14 (35%) |
| | ≥ 6 months | 26 (65%) |
| TLC at presentation | <250 x$10^3$ cells/$mm^3$ | 29 (72.5%) |
| | ≥250 x$10^3$ cells/$mm^3$ | 11 (27.5%) |
| Immuno-phenotyping | ALL pre-B | 22 (55%) |
| | ALL pro-B | 17 (42.5%) |
| | ALL t-cell | 1 (2.5%) |
| KMT2A rearrangement (n =24) | Wild type | 5 (20%) |
| | Rearranged | 19 (80%) |
| CNS status (n =36) | CNS I | 21 (58.3%) |
| | CNS II | 2 (5.6%) |
| | CNS III | 13 (36.1%) |
| Complaints of cases at presentation | Fever | 27 (67.5%) |
| | Pallor | 21 (52.5%) |
| | Bleeding | 3 (7.5%) |
| | Neck swelling | 1 (2.5%) |
| | CNS symptoms | 1 (2.5%) |

TLC: Total Leukocyte count CNS: Central nervous system.

In order to address the clinical features, toxicities, and outcomes for infants with ALL, we retrospectively reviewed 40 patients treated at the NCI in Egypt. We compared the outcomes and toxicities of patients treated on the Interfant-99 chemotherapy protocol versus the St. Jude Total Therapy XV protocol. In the current study, the age of diagnosis was less than six months in 14 cases (35%) and greater than six months in 26 cases (65%), which is comparable to a previous study conducted in Taiwan that reported cases aged < 6 months in 10 infants (43%), and infants aged >6 months in 13 infants (57%). In our research, the male-to-female ratio was 1.7:1, whereas in another study, 52% of the participants were female, and 48% were male (Pieters et al.,2007). TLC was greater than 250x$10^3$ cells/$mm^3$ in 11 (27.5%), which is consistent with previous findings that TLC was greater than 300x$10^3$ cells/$mm^3$ in 27%–30% of infants with ALL (Pieters et al.,2007 & Pieters et al.,2019).

Of a total of 40 patients, KMT2A rearrangement by FISH was done for 24 (60%) patients. It was rearranged in 19 (80%) cases. This is in line with Pieters et al. 2019 who reported that 74% of patients were KMT2A rearranged, and 23% had other KMT2A translocations. Also, Knez et al. 2019 reported that 85% of infants with ALL were KMT2A rearranged. We found that patients with rearranged KMT2A presented at a significantly younger age, less than six months at presentation; 42.1% of rearranged KMT2A patients were less than six months versus none in the wild group, this is in line with Knez et al.,2019 who found that KMT2A rearrangement progressively decreased with age. Also, we found that patients with rearranged KMT2A presented with other unfavorable prognostic factors like high TLC ≥250x$10^3$/$mm^3$ and CNS III, which is in agreement with a study reported that Infants with rearranged KMT2A ALL are typically younger, present with higher white blood cell counts (WBC), have more frequent CNS involvement and a far worse prognosis (Dreyer et al., 2015). The OS and EFS for those with wild type KMT2A were better than rearranged KMT2A, 40% versus 26.3% and 20% versus 5.3% with p value= 0.704 and 0.922, which was in line with a study reported that the presence of rearranged KMT2A has been recognized as an adverse prognostic factor in infant ALL with 3- to 6-year EFS ranges from 5% to 28% (Chen et al.,2010). Infants with KMT2A gene rearrangements received intensified chemotherapeutic regimens with agents that are not typically incorporated into first-line ALL treatment for older children. However, despite these intensified approaches,

**Table 2.** Baseline characteristics of study participants and complications according to treatment protocol

| Protocol of treatment | | Interfant-99 (n=24) | Total XV (n=14) | P value |
|---|---|---|---|---|
| Age at diagnosis | < 6 months | 12 (50%) | 1 (7.1%) | 0.012* |
| | ≥ 6 months | 12 (50%) | 13 (92.9%) | |
| Gender | Male | 14 (58.3%) | 10 (71.4%) | 0.420 |
| | Female | 10 (41.7%) | 4 (28.5%) | |
| TLC group | <250 x$10^3$ cells/$mm^3$ | 13(54.2) | 14(100) | 0.033* |
| | ≥250 x$10^3$ cells/$mm^3$ | 11 (45.8%) | 0 (0%) | |
| CNS status | CNS I | 13 (56.5%) | 8 (61.5%) | |
| | CNS II | 0 (0%) | 2 (15.4%) | 0.104 |
| | CNS III | 10 (43.5%) | 3 (23.1%) | |
| KMT2A | Rearranged type | 17 (94.4%) | 2 (33.3%) | |
| | Wild type | 1 (5.6%) | 4 (66.7%) | 0.006* |
| MRD D33 | ≤ 0.01 | 3 (50%) | 4 (100%) | |
| | > 0.01 | 3 (50%) | 0 (%) | 0.2 |
| MRD end of consolidation | < 0.01 | 0 (0%) | 2 (100%) | |
| | >0.01 | 5 (100%) | 0 (0%) | 0.047* |
| Relapse | Yes | 7 (29.2%) | 3 (21.4%) | |
| | No | 17 (70.8%) | 11 (78.6%) | 0.715 |
| Death | Yes | 16 (66.7%) | 10 (71.4%) | 1.000 |
| | No | 8 (33.3%) | 4 (28.6%) | |
| Infectious toxicities during induction | Gram-negative | 8 (33.3%) | 5 (35.7%) | 0.450 |
| | Gram-positive | 1 (4.2%) | 2 (14.2%) | |
| | Invasive fungal-infection | 3 (12.5%) | 2 (14.3%) | |
| | Febrile neutropenia | 10 (41.7%) | 3 (21.4%) | |
| | No infectious toxicity | 2 (8.3%) | 2 (14.3%) | |
| Non-infectious toxicities during induction | GIT toxicity | 5 (20.8%) | 1 (7.1%) | 0.496 |
| | Cardiotoxicity | 2 (8.3%) | 1 (7.1%) | |
| | CNS toxicity | 2 (8.3%) | 1 (7.1%) | |
| | Respiratory failure | 0 (0%) | 1 (7.1%) | |
| | No toxicity | 15 (62.5%) | 10 (70%) | |
| Infectious toxicities post-induction | Gram-negative | 2 (14.3%) | 1 (25%) | 0.278 |
| | Gram-positive | 4 (28.5%) | 1 (25%) | |
| | Invasive fungal-infection | 2 (14.3%) | 0 (0%) | |
| | Viral-infection | 2 (14.3%) | 0 (0%) | |
| | Febrile neutropenia | 2 (14.3%) | 1 (25%) | |
| | No infectious toxicity | 2 14.3(%) | 1 (25%) | |
| Noninfectious toxicities post-induction | Hepatotoxicity | 1 (7.7%) | 1 (25%) | 0.106 |
| | GIT toxicity | 1 (7.7%) | 1 (25%) | |
| | Cardiotoxicity | 0 (0%) | 1 (25%) | |
| | No toxicity | 11 (84.6%) | 1 (25%) | |
| Cause of death | Treatment-related | 14 (88%) | 8(80%) | |
| | Disease-related | 2 (12%) | 2(20%) | 0.532 |

TLC: Total Leukocyte count CNS: Central nervous system, MRD: minimal residual disease, GIT: gastric Intestinal tract.
*Statistically significant as p-value < 0.05.

EFS rates for these patients remain poor (Knez et al.,2019). We cannot compare the outcomes of patients with rearranged KMT2A treated with interfant-99 versus those treated with St. Jude Total Therapy XV, as 17 (90%) patients with rearranged KMT2A were treated with interfants-99, and only 2 (10%) patients were treated with St. Jude Total Therapy XV. The coexistence of myeloid-associated antigens and chromosomal rearrangements involving the mixed lineage leukemia (MLL) gene, most commonly arising from the translocation t (4;11) (q21; q23), these considerations have prompted some collaborative groups to develop specific protocols for the management of ALL in infants, such as the international Interfant-99 trial, which used a cytarabine-intensive chemotherapy regimen, with increased exposure to both low- and high-dose

**Table 3.** Baseline characteristics of study participants and protocol of treatment according to KMT2A rearrangement

| | | Rearranged (n=19) | Wild type (n =5) | P value |
|---|---|---|---|---|
| Age at diagnosis (months) | < 6 months | 8 (42.1%) | 0 (0%) | 0.076 |
| | ≥ 6 months | 11 (57.9%) | 5 (100%) | |
| Gender | Male | 10 (52.6%) | 4 (80%) | 0.358 |
| | Female | 9 (47.4%) | 1 (20%) | |
| TLC group | <250 x$10^3$ cells/$mm^3$ | 9(47.4) | 5(100) | 0.064 |
| | ≥250 x$10^3$ cells/$mm^3$ | 10 (52.6%) | 0 (0%) | |
| CNS status | CNS I | 12 (66.7%) | 3 (60%) | 0.145 |
| | CNS II | 0 (0%) | 1 (20%) | |
| | CNS III | 6 (33.3%) | 1 (20%) | |
| protocol of treatment | Interfant-99 | 17 (89.5%) | 1 (20%) | 0.006* |
| | St. Jude Total Therapy XV | 2 (10.5%) | 4 (80%) | |

TLC: Total leukocyte count, CNS: Central nervous system. *Statistically significant as p-value < 0.05.

**Table 4.** Overall survival and event-free survival according to protocols of treatment and baseline characteristics of study participants

| Overall survival | | HR (95% CI) | 3-year OS % | P value |
|---|---|---|---|---|
| Protocol of treatment | Interfant -99 | 0.99 (0.44 – 2.23) | 33.3% | 0.985 |
| | St. Jude Total Therapy XV | 1.01 (0.45 – 2.26) | 28.6% | |
| KMT2A rearrangement | Rearranged | 1.18 (0.35 – 3.97) | 26.3% | 0.704 |
| | Wild type | 0.85 (0.25 – 2.86) | 40% | |
| Age group | < 6 months | 1.75 (0.77 – 3.97) | 14.3% | 0.178 |
| | ≥ 6 months | 0.57 (0.25 – 1.29) | 38.5% | |
| TLC group | <250 x$10^3$ cells/$mm^3$ | 0.57 (0.22 – 1.48) | 33.3% | 0.249 |
| | ≥250 x$10^3$ cells/$mm^3$ | 1.75 (0.67 – 4.53) | 20% | |
| CNS status | CNS I | 0.002 (0.0001 – 0.053) | 33.3% | <0.001* |
| | CNS III | 376.3 (18.8 - 7540) | 0% | |
| **Event free survival** | | HR (95% CI) | 3-year EFS % | P value |
| Protocol of treatment | Interfant -99 | 1.2 (0.58 – 2.49) | 12.5% | 0.627 |
| | St. Jude Total Therapy XV | 0.83 (0.4 – 1.73) | 21.4% | |
| KMT2A rearrangement | Rearranged | 1.05 (0.35 – 3.18) | 5.3% | 0.922 |
| | Wild type | 0.95 (0.31 – 2.85) | 20% | |
| Age group | < 6 months | 1.06 (0.51 – 2.19) | 14.3% | 0.874 |
| | ≥ 6 months | 0.94 (0.46 – 1.95) | 15.4% | |
| TLC group | <250 x$10^3$ cells/$mm^3$ | 0.49 (0.19 – 1.27) | 16.7% | 0.145 |
| | ≥250 x$10^3$ cells/$mm^3$ | 2 (0.79 – 5.11) | 10% | |
| CNS status | CNS I | 0.09 (0.01 – 0.75) | 18% | 0.026* |
| | CNS III | 11 (1.33 – 91.3) | 0% | |

HR: Hazard ratio, CI: Confidence interval, TLC: Total leukocytic count, CNS: Central nervous system, *Statistically significant as p-value < 0.05.

cytarabine during the first few months of therapy (Pieters et al.,2007). While others have used standard risk-adjusted therapy, in which infants frequently meet the criteria for standard or high-risk pediatric patients like St. Jude Total Therapy XV (Pui et al., 2009 & Ferster et al.,2000). A comparison of the Interfant-99 protocols and St. Jude Total Therapy XV in terms of patient prognosis and toxicity is one of the essential aims of this study. The Interfant-99 protocol is considered more intensive and requires more hospitalization to receive chemotherapy and more need for supportive care, which are obstacles in countries with limited hospital beds and resources. We found no significant difference in survival outcomes and toxicities between the two protocols, but the interfant-99 protocol had an increased frequency of febrile neutropenia, 14/24 (50%) versus 4/14 (28%), requiring more hospitalization and supportive care than St. Jude Total Therapy XV.

**Table 5.** Infectious and noninfectious toxicities during treatment in the study participants

| During induction phase of treatment | | | | Patients (n =40) |
|---|---|---|---|---|
| Infectious toxicities | Bacterial | Gram-negative | MDR | 11 (27.5%) |
| | | | ESBL | 2 (5%) |
| | | Gram-positive | MRSA | 2 (5%) |
| | | | CoNS | 1 (2.5%) |
| | Invasive fungal infection | | | 5 (12.5%) |
| | Febrile neutropenia | | | 13 (32.5%) |
| | No significant infectious toxicity | | | 6 (15%) |
| Non-infectious toxicities | Hepatotoxicity | | | 3 (7.5%) |
| | GIT toxicity | | | 3 (7.5%) |
| | Cardiotoxicity | | | 3 (7.5%) |
| | CNS toxicity | | | 3 (7.5%) |
| | Respiratory failure | | | 2 (5%) |
| | No toxicity | | | 26 (65%) |
| Post induction phase of treatment | | | | Patients (n =22) |
| Infectious toxicities | Bacterial | Gram-negative | MDR | 2 (9.1%) |
| | | | ESBL | 1 (4.55%) |
| | | Gram-positive | MRSA | 3 (13.64%) |
| | | | CoNS | 2 (9.1%) |
| | Invasive fungal infection | | | 2 (9.1%) |
| | Viral infections | | | 2 (9.1%) |
| | Febrile neutropenia | | | 3 (13.64%) |
| | No significant infectious toxicity | | | 3 (13.64%) |
| Non-infectious toxicities | Hepatotoxicity | | | 2 (9.1%) |
| | GIT toxicity | | | 2 (9.1%) |
| | Cardiotoxicity | | | 1 (4.55%) |
| | No toxicity | | | 12 (54.55%) |

MDR: multi-drug resistant, ESBL: extended-spectrum beta-lactamases, MRSA: methicillin-resistant Staphylococcus aureus, CoNS: coagulase-negative staphylococci, GIT: gastric Intestinal Tract, CNS: central nervous system.

Regarding infectious toxicities during induction in the present study, 16 (40%) patients had bacterial infections, of which 11 (27%) were gram-negative MDR bacteria. Five (12.5%) patients had an invasive fungal infection, and 13 (32.5%) patients had febrile neutropenia with no documented causative organism. In the present study, 55% of patients were alive after induction, while 45% died during the induction phase. Compared to other studies, who reported that 3.8% of cases died during induction, this percentage is extremely high (Pieters et al.,2007& Pieters et al.,2019). This was consistent with the findings of the COG AALL0631 (NCT00557193) trial, which reported that an intensive induction regimen led to a high induction mortality rate of 15.4%; the trial was subsequently modified to include a less intensive induction and enhanced supportive care guidelines (Salzer et al.,2015). Post-induction phases are also marked by a rise in infectious morbidity. Regarding survival outcome in the present study, 3-years EFS was 14%, and 3-years OS was 26.3%. Unlike other results conducted by Pieters et al. 2007 who found that 4-year EFS was 47.0% and OS was 55·3%. Similarly, Dreyer et al 2015. reported an overall 5-years EFS and OS of 42.3 ± 6% and 52.9 ± 6.5%, respectively. Koh et al 2015. reported an EFS of 4 years, 43.2 ± 6.3, and OS of 4 years, 67.2 ± 6.0. Our results were comparable to other studies conducted in Taiwan and India, which reported that 5-years EFS was 18 ± 10.0 and 2 years 27.3 ±5.0, respectively (Chen et al.,2010 & Das et al.,2014). The outcome of acute leukemia, in general, in LMICs is inferior to that of developed countries, and it varies by country. The difference between our study's mortality and morbidity rates and those of studies conducted in developed countries may be attributable to the late presentation during febrile neutropenia and the diverse antimicrobial bio-gram differences between developed and developing nations.

In developing nations, the general population and hospitals misuse and abuse antibiotics. A

persistent and resistant threat resulting from insufficient antibiotic control and easy population access. Self-medication is a significant contributor to antimicrobial resistance. Therefore, we have gram-negative multidrug-resistant and methicillin-resistant Staphylococcus aureus bacteremia. Piperacillin-tazobactam was the empirical antibiotic administered to a patient with febrile neutropenia. On the basis of the results of a blood culture, the antibiotic was subsequently altered.

Our relatively humid climate facilitates the growth of microorganisms and increases the incidence of fungal infections. Additionally, the difficulty in establishing venous access in such young patients; this difficulty resulted from their young age and low body weight. In our study, we found that 78% of death were attributable to infection and sepsis; this was consistent with another study conducted in Taiwan, which found that approximately 80% of deaths that occurred during therapy were related to infection; and is comparable to what has been reported in previous studies (Chen et al.,2010 &, Rubnitz et al., 2004). This elevated mortality may be owing in part to more intensive regimens and an increase in infant susceptibility to infection. More effective prophylactic antibiotics, early recognition of risk factors and signs of severe infection, and more aggressive supportive care may contribute to an improvement in outcomes. MDR gram-negative bacteria are the leading cause of infections that result in sepsis and mortality at our institution; as a result, we have implemented preventative measures such as hand hygiene and antimicrobial stewardship programs to reduce the prevalence of resistance mechanisms.

Patients colonized with MDR gram-negative bacteria have a high risk of developing a bloodstream infection as a result of these bacteria. Thus, in our institution with a high infection rate, we are considering implementing a screening program consisting of rectal swabs for all patients during each cycle of chemotherapy to detect colonization with these organisms and modifying the empirical antibiotics treatment of colonized patients. During an episode of febrile neutropenia, all patients colonized with MDR gram-negative bacteria received empirical treatment with a high dose and prolonged infusion of meropenem, amikacin, and colistin, which was de-escalated or escalated according to blood culture results. The small sample size, the need for cytogenetic and molecular studies for disease follow-up, and the loss of some data from medical records were some factors that limit our study.

In conclusion, the survival outcome in our studied patients is significantly lower than the results of comparable studies conducted in developed countries but is closely comparable to similar studies conducted in developing countries. Patients who presented with an age less than six months, TLC > $250x10^3$ cells/$mm^3$, KMT2A rearrangement, and CNSIII had a higher hazard risk and a lower percentage of OS and EFS. There was no difference in survival outcome or toxicities between the interfant-99 protocol and St. Jude Total Therapy XV, but the interfant-99 protocol was associated with more episodes of febrile neutropenia, necessitating supportive care and hospitalization. High treatment-related mortality in this age group highlights the need for an effective system of supportive care for such a vulnerable group of patients.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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No fund was received for this work.

## AUTHORS' CONTRIBUTION

All authors contributed to the design of work, analysis, and interpretation of data, drafting and revision of the manuscript. The manuscript was finally approved by all authors.

## AVAILABILITY OF DATA

The data that support the findings of this study are available from the corresponding author, [Ali N] upon reasonable request.

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