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The Outcome of Infants with Acute Lymphoblastic Leukemia Treated with Interfant-99 Protocol

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Authors' contributions

This work was carried out in collaboration between both authors. Author GB performed and manage the statistical analysis, wrote the protocol. Author PS designed the study, managed the literature searches and wrote the first draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: The Outcome of Infants with Acute Lymphoblastic Leukemia Treated with Interfant-99 Protocol
Materials and Methods: In this retrospective analytical study, all newly diagnosed infants with ALL who were treated with Interfant-99 protocol from 2004 to 2014 in Ali-Asghar Children's Hospital in Tehran were included. Demographic data including age at diagnosis, sex, initial WBC, Hb and platelet count, flow cytometric diagnosis, cytogenetic findings, follow-up duration, and their outcome was extracted from patients' medical records. All the above data were analyzed by SPSS 23 software.
Results: 11 infants with ALL (5 girls and 6 boys) were included in the study. Mean and median age at diagnosis of all enrolled patients were 7.20 (std. deviation = 1.78; range = 3.57-9.37) and 7.90 months, respectively. 5 of the 11 patients had t (4; 11) and all of them were Pro-B ALL. The mean

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initial WBC in patients with this translocation was significantly higher than the others (193400 vs. 49166), and this difference was statistically significant (P = 0.004) despite the small number of patients under study. None of the patients had CNS involvement or mediastinal mass at diagnosis. Three patients relapsed, two of whom had isolated CNS relapse. Finally, one of them recovered completely as chemotherapy continued, another suffered a bone marrow relapse and eventually died, and a third suffered a bone marrow relapse and died about 10 months after relapse. The median follow-up of all patients was 53.83-mo. The estimated 5-yr overall survival of patients was 68.60% ± 15.10, and their Estimated 5-yr event-free survival was 21.20%±45.70. Infection was the most common complication during treatment that was manageable.

Conclusion: The Interfant-99 protocol appeared to improve the outcome of infants with ALL even with t (4; 11), with manageable complications. However, its implementation in developing countries has problems due to the small number of rooms suitable for heavy chemotherapy, and the dose of drugs that should be modified. It is worth noting that proving this requires a comprehensive prospective study with an appropriate sample size.

Keywords: Outcome; infant; acute lymphoblastic leukemia; interfant-99.

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is rarely seen in infants less than one year and behaves biologically different from older children. Specific markers for this disease in this age group are: 1. High frequency of abnormalities on chromosome 11q23 affected by mixed lineage leukemia (MLL) gene, 2. Pro B-cell phenotype without CD10 expression,3. High tumor load at presentation [1,2]. Unfortunately, the outcome for this group of patients has been disappointing compared to older children with ALL [3-12]. These infants are more resistant to conventional chemotherapy regimens [13,14]; however, Cytarabine has been very effective in treating them [14,15]. For example, one study found that infants with Pro-B ALL had a better outcome after receiving post-remission treatment with high-dose cytarabine [3]. Risk factors for prognosis in these infants include: t (4; 11), age at diagnosis, white blood cell count at diagnosis, CNS involvement at diagnosis, the incidence of CD10, coexpression of myeloid markers, and early response to prednisolone [1,2,7,8,15]. An early response to prednisolone clearly provides a good prognosis at the start of treatment[5]. To this end, BFM group introduced a new chemotherapy regimen called Interfant-99 with the approach of using High dose Methotrexate (HDMTX) and high dose cytarabine (HDAC) in the consolidation phase and VP16 pulses during maintenance. Another difference with this regimen is the elimination of intrathecal chemotherapy during the second maintenance phase.

During the last two decades since the introduction of this protocol, other chemotherapy regimens have been proposed for this group of patients. These regimes more or less claim to improve the outcome of these patients. Therefore, the survival of these patients can be increased by examining the outcomes of using the Interfant-99 protocol in other medical centers, especially in developing countries, and comparing it with other protocols.

Based on the above, in this case series study, the outcome of the treatment of these patients with this protocol in our medical center was evaluated.

2. MATERIALS AND METHODS

In this case series retrospective analytical study, all newly diagnosed infants with ALL who were treated with Interfant-99 protocol from 2004 to 2014 in Ali-Asghar Children's Hospital in Tehran were included. Demographic data including age at diagnosis, sex, initial WBC, Hb and platelet count, flow cytometric diagnosis, cytogenetic findings, follow-up duration, and their outcome was extracted from patients' medical records. All the above data were analyzed by SPSS 23 software.

Patients' outcome was calculated and recorded using the Kaplan-Meier (KM) method as overall survival (OS) (patient survival time from diagnosis regardless of any disease outcome) and Event-free survival (EFS) (patient survival time from diagnosis without any relapse and residual disease in complete remission). In comparative studies, P values of less than 0.05 were significant.

3. RESULTS

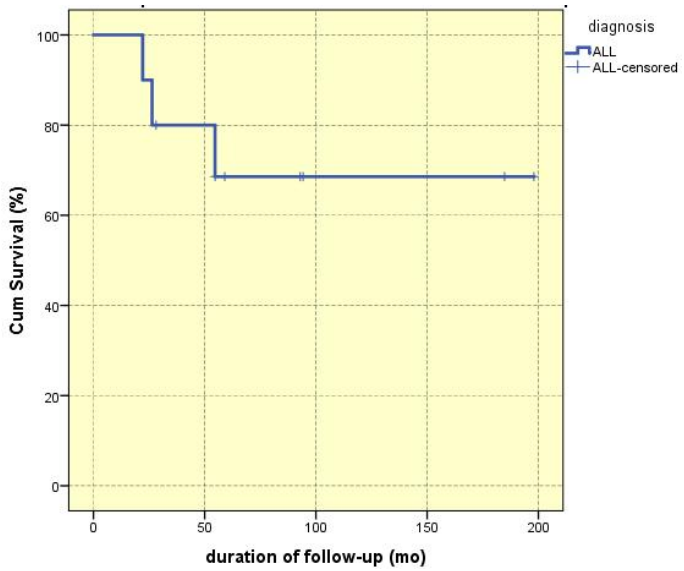
11 infants with ALL (5 girls and 6 boys) were included in the study. Mean and median age at diagnosis of all patients were 7.20 (std. deviation = 1.78; range = 3.57-9.37) and 7.90 months, respectively. The mean age at diagnosis was higher in boys than in girls (8.46 vs 6.45 months), but this difference was not statistically significant (P = 1.26). The mean initial WBC count was 114727 / µl (5000-250000). There was no significant difference in this count between girls and boys. In addition, the mean hemoglobin count of patients at diagnosis was 8.4 g / dl (2.9-12.4). This count was higher in boys than girls (8.9 vs 7.8), but there was no statistically significant difference between them (P = 0.56). The mean platelet count of patients was 74454 / µl (10000-258000) which was nearly 1.8 times higher in girls than in boys (97600 vs 55166), but this difference was not statistically significant (P = 0.40). Five out of 11 patients (3 boys and 2 girls) had a t (4; 11) and all were Pro-B ALL. Two patients had T-cell ALL and 4 had B-precursor ALL. The mean initial WBC in patients with this translocation was significantly higher than the others (193400 vs 49166), and this difference was statistically significant (P = 0.004) despite the small number of patients under study. The mean hemoglobin count at diagnosis in the group with this translocation was lower than other patients (6.8 vs 9.7), but this difference was not statistically significant (P = 0.11). In addition, the mean platelet count of patients with t (4; 11) was slightly higher than the half the mean of other patients (51200 vs 93833), but this difference was not statistically significant (P = 0.40). None of the patients had CNS involvement or mediastinal mass at diagnosis. Three patients relapsed, two of whom had isolated CNS relapse. Finally, one of them recovered completely as chemotherapy continued, another suffered a bone marrow relapse and eventually died, and a third suffered a bone marrow relapse and died about 10 months after relapse. The median follow-up of all patients was 53.83-mo and their estimated 5-yr OS and EFS was 68.60 ± 15.10% (Graph 1 and 2).

It should be noted that one of the patients, who was from Afghanistan, forced to leave Iran two months before the end of chemotherapy, where he died of acute gastroenteritis. One patient did not return due to family disputes 10 months after starting treatment and was not included in the survival analysis. The estimated 10-yr OS and EFS of patients was 68.60 ± 15.10% and 45.70 ± 21.20%, respectively (Graph 1 and 2). Infection was the most common complication during treatment that was manageable.

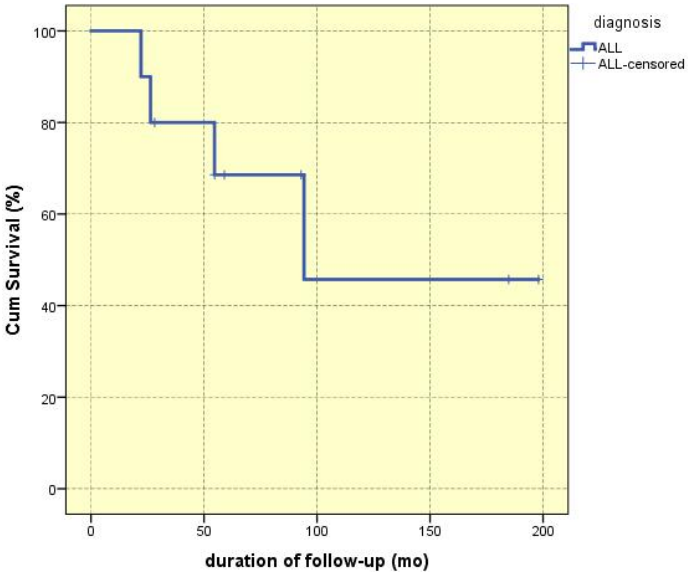
Table 1. Patients characteristics and outcome

Number	Gender	Age at diagnosis (mo)	Flowcytometric diagnosis	Cytogenetic findings	Initial WBC (/µl)	Initial Hgb (gr/dl)	Initial Platelet (/µl)	BM status (end of induction)	Follow up duration (mo)	Final Outcome	Complete remission/Relapse
1	M	8.00	Pre-B ALL	NI	120000	7.5	15000	M1	198	A	CR
2	F	7.00	Pre-B ALL	NI	45000	8.0	45000	M1	185	A	CR
3	M	4.50	Pro-B ALL	t(4;11)	250000	6.5	25000	M1	26	D	R
4	F	6.03	Pro-B ALL	t(4;11)	230000	5.0	30000	M1	22	D	R
5	M	7.83	T-cell ALL	NI	5000	12.4	90000	M1	93	A	CR
6	F	3.57	Pro-B ALL	t(4;11)	220000	2.9	10000	M1	10	U	U
7	F	7.90	T-cell ALL	t(7;9)	87000	10.5	145000	M1	94	A	R
8	F	8.33	Pre-B ALL	NI	5000	12.4	258000	M1	59	A	CR
9	M	8.33	Pro-B ALL	t(4;11)	85000	10.4	43000	M1	55	A	CR
10	M	8.33	Pro-B ALL	t(4;11)	182000	9.0	148000	M1	55	D	R
11	M	9.37	Pre-B ALL	NI	33000	7.5	10000	M1	28	A	CR

M: male; F: female; mo: month; NI: normal; M1: Blast less than 5% in marrow; A: alive; D: dead; U: unknown; CR: complete remission; R: relapse



Graph 1. Estimated overall survival of all enrolled patients



Graph 2. Estimated event-free survival of all enrolled patients

4. DISCUSSION

Infants with ALL have long had a poor prognosis [1-12]. The results of bone marrow transplantation in infants with ALL with t (4; 11) were also not promising [17]. In addition to the age of patients at the time of disease onset being as an independent poor prognostic factor, the high prevalence of t (4; 11) in these patients is an independent factor in reducing their survival [16-18]. Moreover, the high prevalence of Pro-B-cell ALL among this group of patients affects their poor prognosis due to prednisolone poor response. Another prognostic factor that independently affects the poor prognosis of these patients is CNS disease at diagnosis [18-19]. Therefore, the treatment of this group of patients was one of the problems of research groups to find the best treatment protocols for many years, especially since the use of radiotherapy during treatment is not possible due to their young age. As a result, the introduction of chemotherapy protocols with the aim of increasing the long-term survival of these patients is of higher importance.

Interfant-99 is one of these protocols developed by the BFM Group for this purpose. The obvious changes in this protocol are the addition of High dose Methotrexate at 5 g / m^2 on days 1 and 8, and high dose Cytarabine at 3 g / m^2 every 12 hours on days 15, 16, 22 and 23 in the consolidation phase. The first report on the outcome of infants with ALL treated with this protocol was published in 2007 by Rob Pieters et al. [18]. This study was performed on 482 patients, half of whom were under the age of 6 months at diagnosis. About 67% of patients were in the standard-risk group and 31% in the high-risk group. About 53% of patients had t (4; 11) and about 57% had Pro-B-cell ALL. 5-yr OS and 5-yr EFS of all patients were 53.80 ± 3.00% and 46.40 ± 2.70%, respectively. 20 years of experience treating infants with ALL was presented in a study by Amanda Ibagy et al. [20]. During 1990-2010, they analyzed 41 patients treated with conventional, Interfant-99, and IC-BFM2002 protocols, and did not achieve promising results because about 70% of patients often died of septic shock.

Later, with the introduction of the Interfant-06 chemotherapy regimen and the use of myeloid-type chemotherapy postinduction, the BFM group failed to increase patient survival compared to Interfant-99, which used the lymphoid-type course IB postinduction chemotherapy. Georg Mann et al. (2016) for 297 infants with ALL and t (4; 11) treated with the Interfant-99 protocol presented HSCT results [21]. They concluded that for the group less than 6 months old at diagnosis and prednisolone poor response, HSCT seemed to be better than chemotherapy alone, and it was not different from chemotherapy alone for patients older than 6 months at diagnosis and prednisolone good response.

Other study groups have not provided better results than BFM group. EORTC-Childhood Leukaemia Cooperative Group was treated 25 enrolled patients with EORTC-CLCG protocol and 4-yr EFS of them was 43%[6]. The Pediatric Oncology Group experience on 82 enrolled patients with using POG 8493 chemotherapeutic regimen was dismal and 4-yr EFS of all enrolled patients was only 28%. The outcome of 135 infant with ALL treated by CCG-1883 protocol was not better than other regimens and 4-yr OS and EFS of them were 51% and 39%, respectively [8]. The result of UKALL-92 protocol on 86 enrolled patients was not promising and 5-yr OS and EFS of them were 46% and 33%, respectively [9]. The Children's Oncology Group treated 115 patients with the CCG-1953 protocol and were able to only get 45% of 5-year OS and 42% 5-yr EFS [7]. Of course, another protocol was introduced from Japan based on the presence or absence of KMT2A gene rearrangement called JPLSG MLL-10, and they were able to significantly increase survival [22].

Despite the very small number of patients in the present study, which was due to the low incidence of this disease in infancy and the single-focus study, the results were acceptable compared to other studies. None of the patients died of infection for as long as they were under our control. Perhaps the reason for those brief changes was that we made in the protocol. We modified dose of drugs and calculated them based on body weight rather than body surface area, reduced the high dose Cytarabine from 3 g / m^2 / dose to 1 g / m^2 / dose and added intrathecal Cytarabine to it. However, proving this requires a comprehensive prospective study with an appropriate sample size. Additionally, there was no information on the status of KMT2A gene rearrangement in patients under study.

5. CONCLUSION

The Interfant-99 protocol appeared to improve the outcome of infants with ALL even with t (4; 11), with manageable complications. However, its implementation in developing countries has problems due to the small number of rooms suitable for heavy chemotherapy, and the dose of drugs that should be modified. It is worth noting that proving this requires a comprehensive prospective study with an appropriate sample size.

CONSENT

As per international standard, parental written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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