Survival Rate of Childhood Leukemia in Shiraz, Southern Iran

Almasi-Hashiani, Amir¹, MSc; Zareifar, Soheil², MD; Karimi, Mehran², MD; Khedmati, Esmaeil³, MSc; Mohammadbeigi, Abolfazl⁴, PhD

1. Department of Public Health, School of Health, Arak University of Medical Sciences, Arak, Iran
2. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
3. Center for Research on Social Determinants of Health, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
4. Department of Public Health, School of Health, Qom University of Medical Sciences, Qom, Iran

Abstract

Objective: Leukemia is the most prevalent type of cancer in children. The aim of this study was to estimate the 5-year survival rates of Acute Lymphoblastic Leukemia (ALL) and Acute Myeloblastic Leukemia (AML) as well as factors influencing them.

Methods: This is a nonrandomized retrospective study conducted on 280 patients with ALL and AML. They were all below 15 years old children admitted to Shahid Faghihi hospital, Shiraz, Iran from 2004 to 2008. The survival rates were estimated by applying the Kaplan-Meier method. In addition, the log rank test was used to estimate the statistical significance of differences in the survival probability. Cox regression model was applied to conduct multivariate analysis for adjusting confounding variable. All analyses were performed in SPSS statistical software (version 16). \( P \) values less than 0.05 were considered as statistically significant.

Findings: The mean (± standard deviation) of the observation period was 28.2±16.1 months. In this period, 60 (24.7%) patients (47 ALL and 15 AML) passed away. The cumulative rate of survival in this study was 53.3±0.1 percent. This probability was 56.6±0.1% and 44.2±0.1% for ALL and AML patients, respectively, which indicates no statistically significant difference between them (\( P=0.8 \)). According to Cox model, there was a significant relationship among the variables of platelet count and relapse with the survival rate.

Conclusion: Platelet count was identified as a positive prognostic factor of the survival rate in ALL patients. However, on the base of our results and other studies, incidence of relapse and the number of relapses are significant factors of survival rates of leukemia.

Key Words: Lymphoblastic Leukemia; Myeloblastic Leukemia; Survival Rate; Relapse

Introduction

Cancer, after non-intentional injuries, is ranked as the second most common cause of mortality in under 14 year old children (e.g. by rate of 0.41 deaths per 10,000, in Italy)\(^1\). Despite the low rate of overall incidence, leukemia is the most prevalent type of cancer in children\(^2-8\), in a way that almost 32% of pediatric cancers consist of leukemia\(^9\). The most common type of leukemia in children under 19 years is Acute Lymphoblastic Leukemia (ALL), and its incidence in 1-4 year-old children is over nine times more than in 20-24 year-old individuals\(^10\). In developed countries, ALL is also responsible for almost 80% of childhood leukemia cases\(^3,11\), and its incidence rate reaches to 34.3 cases per one million\(^3\). Far differently, Acute Myeloblastic Leukemia (AML)
cases in children are very rare, and its annual incidence in Europe is limited to 4 to 9 cases per million. Moreover, only 20-25% of all newly-diagnosed leukemia cases in children under 15 years are of AML and CML (ranging from 300 to 350 annual new cases in European Union)[12], and its incidence rate reaches hardly 7.1 to 8.9 cases per million[3]. The survival rates of childhood cancers have significantly improved in recent decades[1,13]. In America, for instance, advances in cancer therapeutic procedures and supportive cares have resulted in elevation of the five-year survival rate from less than 30% in 1960 to over 70% in 1990[13].

The survival rate of all childhood cancers has been investigated in many studies. In a study carried out by Sankila and colleagues[14], starting 1988 to 1997 in Europe, the five-year survival rate was estimated as 37%, while this rate was calculated as 74% in American patients who were diagnosed between 1985 and 1999. In the study conducted in Shiraz in 2002, from 75 ALL patients diagnosed during 1995-2000, five-year survival rate was estimated as 72.5%[4].

Considering the soaring trend in incidences and prevalence rates of leukemia, in this study we intended to estimate the five-year survival rates of AML and ALL leukemia as well as their influencing factors in children under 15 years who were referred to Shahid Faghihi hospital, Shiraz, Iran from 2004 to 2008.

Subjects and Methods

The subjects of this retrospective study were AML and ALL patients under 15 years who had been hospitalized in Shahid Faghihi hospital from autumn 2004 to autumn 2008. Diagnosis was based on the international coding diseases (ICD-10) with codes C-92 and C-95. Totally 280 patients had been hospitalized during this time. The exact date of the diagnosis - based on immune-phenotyping results - and the exact date of death were considered as the initial event and the end point event, respectively. In cases in which the end point event did not occur due to termination of the study, missed follows, or the patient’s death by reasons other than AML or ALL, data was considered as censored.

The required data was gathered from archived profiles of Shiraz Shahid Motahari Clinic, and the information needed for determining the patients’ survival status was gathered from physician reports, existing profiles, and in some cases, by communicating parents using the recorded phone numbers in the patients’ profiles. Since the required information was obtained from the patients’ profiles which were supplied for research tasks, there were no ethical predicaments in this project. However, the study protocol was approved by ethical committee of Shiraz University of Medical Sciences. Kaplan-Meier method and Log rank test were used to determine the survival rate and to compare the survival curves, respectively. Cox regression model was used to conduct the data modeling (Control of confounding variable). The proportionality assumption (as one of the Cox regression model assumptions) was also studied and confirmed in the variables of interest. The variables with \( P \)-values below 0.25 in univariate analysis and a satisfying proportionality assumption, were qualified to be included in the Cox regression model analysis. Data analysis was performed applying the SPSS statistical software (version 16), and the proportionality assumption was investigated by using the STATA software (version 9). \( P \)-values less than 0.05 were considered as statistically significant.

Findings

From 280 hospitalized patients, 243 (86.7%) cases were successfully followed up until the end of the study. From these successfully followed-up patients, 179 (73.7%) cases were diagnosed as ALL patients and 64 (26.3%) as AML patients. Demographic characteristics of the patients - based on age, gender, residency, and hematologic data - are shown in Table 1. The mean age of ALL patients was 6.8±3.5 years (9.8% males and 40.2% females). Also, the mean age of AML patients was 8.5±3.6 years (53.1% males and 49.6% females). In addition, the mean±SD (median) of the following period was about 28.2±16.1 (22.9) ranging from 6.4 to 67.4 months. During this
Table 1: Demographic characteristics of ALL and AML patients based on age, gender, residency, and hematologic data

| Variables               | Subgroups        | ALL (%) | AML (%) |
|-------------------------|------------------|---------|---------|
| **Age groups**          |                  |         |         |
| >1 yrs                  |                  | 1(0.6)  | 1(1.6)  |
| 1-4.99 yrs              |                  | 65(36.3)| 11(17.2)|
| 5-9.99 yrs              |                  | 58(38.8)| 23(35.9)|
| 10-14.99 yrs            |                  | 45(25.1)| 29(45.3)|
| **Sex**                 |                  |         |         |
| Male                    |                  | 107(59.8)| 34(53.1)|
| Female                  |                  | 72(40.2)| 30(46.9)|
| **Residency**           |                  |         |         |
| Shiraz city             |                  | 63(35.2)| 22(34.4)|
| Fars except Shiraz     |                  | 68(38)  | 23(35.9)|
| Other provinces         |                  | 48(26.8)| 19(29.7)|
| **White blood cell**    |                  |         |         |
| <25000                  |                  | 170(95)| 59(92.2)|
| 25000-49999             |                  | 3(1.7)  | 2(3.1)  |
| 50000-99999             |                  | 3(1.7)  | -       |
| >100000                 |                  | 2(1.1)  | 3(4.7)  |
| **Hemoglobin**          |                  |         |         |
| Abnormal                |                  | 128(71.5)| 54(84.4)|
| Normal                  |                  | 51(28.5)| 10(15.6)|
| **Platelet**            |                  |         |         |
| Thrombocytopenia        |                  | 103(57.5)| 52(81.2)|
| Normal                  |                  | 63(35.2)| 11(17.2)|
| Thrombocytosis          |                  | 13(7.3) | 1(1.6)  |
| **Relapse**             |                  |         |         |
| Yes                     |                  | 61(34.4)| 20(31.2)|
| No                      |                  | 118(56.9)| 44(68.8)|
| **Number of relapses**  |                  |         |         |
| 0                       |                  | 118(65.9)| 44(68.8)|
| 1                       |                  | 36(20.1)| 9(14.1) |
| ≥ 2                     |                  | 25(14)  | 11(17.2)|
| **Immunophenotype**     |                  |         |         |
| Pre B-Cell              |                  | 73(40.8)| -       |
| Common                  |                  | 89(49.7)| -       |
| AML                     |                  | -       | 64(100) |
| T-Cell                  |                  | 17(9.5) | -       |
| **Status**              |                  |         |         |
| Censored                |                  | 132(73.7)| 49(76.6)|
| Death                   |                  | 47(26.3)| 15(23.4)|
| **Total cases**         |                  | 179(73.7)| 64(26.3)|
| **Follow up duration (month) (mean±SD)** | | 28.5(16.3) | 27.4(15.7) |

ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia

period, 60 (24.7%) cases passed away (47 ALL and 15 AML patients). In this study, the cumulative probability of five-year survival rate of cancer was 53.3±0.1% and as Fig. 1 shows, this probability was 56.6±0.1% and 44.2±0.1% for ALL and AML patients, respectively, which indicates no statistically significant differences between them (P=0.8).

According to the log rank test results – shown in Table 2 – in ALL patients, the variables of blood platelet count, relapse history of the disease, and the number of relapses showed a significant relationship with the cancer survival rate; while in AML patients, the survival rate only showed a significant relationship with the relapse history of the disease and the number of relapses. Overall, the survival rate of leukemia (including both ALL and AML subtypes) showed a statistically significant relationship with the platelet count, the relapse history, and the number of relapses.

The results of multivariate analysis, carried out by Cox regression model, are shown in Table 3. As this table illustrates, in ALL patients, variables of platelet count and the number of relapses showed a significant relationship with the cancer survival rate. Moreover, taking both subtypes of leukemia into account, Cox regression model showed a significant relationship among variables of platelet count, number of relapses, and the survival rate.
Discussion

During recent decades, salient advances have been achieved in childhood cancer therapy. Nonetheless, childhood cancers – especially blood cancers – have already been ranked as one of the most common causes of childhood mortality[15]. In this study, we tried to investigate some factors including age, gender, immunophenotype, WBC count, platelet count, and relapse history, which affect ALL and AML patients’ five-year survival rate. In this study, there was no significant relationship between age and survival rate whereas in a study which was conducted by Pastore and colleagues in Italy, children belonging to the 5-9 year-old and the 10-14 year-old groups had, respectively, 30% and 50% risk of death in comparison to the children of the 1-4 year-old

Table 2: The mean of survival rates for ALL, AML, and all patients

| Variables                      | ALL   | P value | AML   | P value |
|--------------------------------|-------|---------|-------|---------|
| Age groups                     |       |         |       |         |
| 1-4 yrs                        | 51.4  | 0.2     | 48.6  | 0.09    |
| 5-9 yrs                        | 46.5  |         | 48.6  |         |
| 10-14 yrs                      | 48.7  | 0.2     | 54.3  |         |
| Sex                            |       |         |       |         |
| Male                           | 49.7  | 0.8     | 46.4  | 0.9     |
| Female                         | 49.9  |         | 47.6  |         |
| Residency                      |       |         |       |         |
| Shiraz city                    | 46.9  | 0.4     | 43.9  | 0.4     |
| Fars except Shiraz             | 51.9  |         | 52.4  |         |
| Other province                 | 46.6  |         | 46.5  |         |
| Initial white blood cell       |       |         |       |         |
| Leukopenia                     | 49.1  | 0.4     | 46.8  | 0.8     |
| Normal                         | 55.8  |         | 51.5  |         |
| Leukocytosis                   | 40.3  |         | 47.3  |         |
| Initial Hemoglobin             |       |         |       |         |
| Abnormal                       | 47.5  | 0.2     | 45.6  | 0.1     |
| Normal                         | 56.4  |         | 57    |         |
| Initial Platelet               |       |         |       |         |
| Thrombocytopenia               | 44.7  | 0.004   | 48.3  | 0.9     |
| Normal                         | 59.8  |         | 45.7  |         |
| Thrombocytosis                 | 34.7  |         | 34.7  |         |
| Relapse                        |       |         |       |         |
| Yes                            | 37.9  | <0.001  | 37.1  | 0.002   |
| No                             | 58.6  |         | 54.2  |         |
| Number of relapses             |       |         |       |         |
| 0                              | 58.6  |         | 54.2  |         |
| ≥ 2                            | 44.7  | <0.001  | 46.3  | <0.001  |
| 28.2                           |       |         | 30.5  |         |
| Immuno-phenotype               |       |         |       |         |
| Pre B-Cell                     | 40.8  | 0.19    | 40.8  |         |
| Common                         | 54.1  |         | 54.1  |         |
| AML                            | -     |         | -     |         |
| T-Cell                         | 45.1  |         | 45.1  |         |

ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia
Table 3: The modeling of risk factors which are effective in the leukemia survival rate by using Cox regression model

| Leukemia type | Variables | Sub groups | Hazard ratio(HR) | 95% CI for HR | P-value |
|---------------|-----------|------------|-----------------|---------------|---------|
| **Total (243 cases)** | Initial Platelet | Normal | 1 | - | - |
| | | Thrombocytopenia Thrombocytosis | 2.41 | 1.1-4.9 | 0.016 |
| | | | 4.54 | 1.4-13.9 | 0.008 |
| | Number of relapses | 0 | 1 | - | - |
| | | 1 | 2.9 | 1.4-5.7 | 0.002 |
| | | ≥ 2 | 7.9 | 4.3-14.5 | 0.001 |
| **ALL (179 cases)** | Initial Platelet | Normal | 2.8 | 1.2-6.4 | 0.012 |
| | | Thrombocytopenia Thrombocytosis | 4.01 | 1.4-14.1 | 0.03 |
| | Number of relapses | 0 | 1 | - | - |
| | | 1 | 2.93 | 1.37-6.29 | 0.006 |
| | | ≥ 2 | 7.53 | 3.71-15.25 | 0.001 |
| **AML (64 cases)** | Relapses | No | 1 | - | - |
| | | Yes | 5.18 | 1.6-16.5 | 0.005 |

ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; CI: Confidence interval

Although a higher survival rate is expected to be observed in females compared to males, our study showed similar rates for both sexes which were in line with the results of the study by Pastore and colleagues[16]. Immunophenotyping results in ALL patients revealed enhanced survival rates for Common ALL patients compared to other patients; however, the differences were not statistically significant.

It has been demonstrated by numerous studies that WBC count has an effective role in survival rate of leukemia, especially ALL patients, in a way that WBC count less than 10,000 is associated with a better prognosis[17]. In our study, although the patients (especally ALL patients) with high levels of leukocytosis, compared to the control group or the patients with leukopenia, showed low rates of survival rates (40.3 months vs. 55.8 and 49.1 months), this difference was not statistically significant. This matter might be due to gathering the WBC count results in the middle of the chemotherapy or other therapies.

As we expected, the incidence of relapse and the number of relapses showed a significant relationship with survival rates for ALL and for AML. In this regard, frequent relapses and nervous system involvement are emphasized as important prognostic factors of survival rate in ALL patients[15,18]. Furthermore, in this study, the variable of platelet count was identified as a positive prognostic factor of the survival rate in ALL patients.

Conclusion

Regardless of some differences between effective factors in prognosis and survival rates of childhood leukemia in different regions of the world, it can be concluded that – according to many studies – indicators such as the disease relapse and the number of relapses as well as factors such as WBC primary count, gender, and immunophenotype play major role in determining the survival rate of leukemia patients. Platelet count was identified as a positive prognostic factor of the survival rate in ALL patients. On the base of our results and other studies, incidence of relapse and the number of relapses are significant factors in survival rate of leukemia.

Acknowledgment

The authors are very grateful for the patients who participated in the study and cooperated with the researchers.

Conflict of Interest: None

References

1. Pession A, Dama E, Rondelli R, et al. Survival of children with cancer in Italy, 1989-98. A report from the hospital based registry of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Eur J Cancer 2008;44(9):1282-9
2. Rajaraman S, Ranganathan R, Viswanathan S. Childhood cancers in Chennai, India, 1990–2001:
Incidence and survival. Int J Cancer 2008;122(11):2607-11.

3. Goubin A, Auclerc MF, Auvrignon A, et al. Survival in France after childhood acute leukemia and non-Hodgkin’s lymphoma (1990–2000). Eur J Cancer 2006;42(4):534-41.

4. Karimi M, Yarmohammadi H, Sabri MR. An analysis of prognostic factors and the five-year survival rate in childhood acute lymphoblastic leukemia. Med Sci Monit 2002;8(12):792-6.

5. Desandes E, Berger C, Tron I, et al. Childhood cancer survival in France, 1990-1999. Eur J Cancer 2008;44(2):205-15.

6. Ou SX, Han D, Severson RK, et al. Birth characteristics, maternal reproductive history, hormone use during pregnancy, and risk of childhood acute lymphocytic leukemia by immunophenotype (United States). Cancer Causes Control 2002;13(1):15-25.

7. Podvin D, Kuehn CM, Mueller BA, et al. Maternal and birth characteristics in relation to childhood leukemia. Paediatr Perinat Epidemiol 2006;20(4):312-22.

8. Belson M, Kigsley B, Holmes A. Risk Factors for Acute Leukemia in Children: A review. Environ Health Perspect 2007;115(1):138-45.

9. The Leukemia and Lymphoma Society. Facts 2007–2008 [Monograph on the Internet]. White Plains NY: Leukemia and Lymphoma Society. Available at: http://www.leukemia-lymphoma.org/attachments/National/br_1182779969.pdf. Access date: Oct 28, 2012.

10. Karimi M, Mehrabani D, Yarmohammadi H, et al. The prevalence of signs and symptoms of childhood leukemia and lymphoma in Fars Province, Southern Iran. Cancer Detect Prev 2008;32(2):178-83.

11. Coebergh JW, Pastore G, Gatta G, et al. EUROCARE Working Group. Variation in survival of European children with acute lymphoblastic leukemia, diagnosed in 1978-1992: the EUROCASE study. Eur J Cancer 2001;37(6):687-94.

12. Gatta G, Luksch R, Coleman MP, et al. EUROCARE Working Group. Survival from acute non-lymphocytic leukemia (ANLL) and chronic myeloid leukemia (CML) in European children since 1978: a population-based study. Eur J Cancer 2001;37(6):695-702.

13. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the childhood cancer survivor study: A multi-institutional collaborative project. Med Pediatr Oncol 2002;38(4):229-39.

14. Sankila R, Martos Jiménez MC, Miljus D, et al. Geographical comparison of cancer survival in European children (1988–1997): Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42(13):1972-80.

15. Pui CH, Schrappe M, Ribeiro RC, et al. Childhood and adolescent lymphoid and myeloid leukemia. Hematology Am Soc Hematol Educ Program 2004;1:118-45.

16. Pastore G, Viscomi S, Gerov GL, et al. Population based survival after childhood lymphoblastic leukemia in time periods corresponding to specific clinical trials from 1979 to 1998 - a report from childhood cancer registry of Piedmont (Italy). Eur J Cancer 2003;39(7):952-60.

17. Hussein H, Sidhom I, Naga SA, et al. Outcome and prognostic Factors of acute lymphoblastic Leukemia in children at the National cancer institute, Egypt. Pediatric Hematol oncol 2004;26(8):507-14.

18. Tsurusawa M, Yumura-Yagi K, Ohara a, et al. Survival Outcome after the First Central Nervous System Relapse in Children with Acute Lymphoblastic Leukemia: A Retrospective Analysis of 79 Patients in a Joint Program Involving the Experience of Three Japanese Study Groups. Int J Hematol 2007;85(1):36-40.