Features of Childhood Acute Myeloid Leukemia in Iran: a Report from Double Center Study

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Abstract- Acute Myeloblastic Leukemia is one of the important malignancies in children. For better managing the prognosis of this disease, there should be enough information about common features of this malignancy. The aim of this study was to evaluate these common features in children with Acute Myeloblastic Leukemia. A total of 104 eligible children less than 15-year-old have been referred from 2007-2011 to two referral centers for childhood malignancies. Basic epidemiological information recorded in checklists for each individual. Analyzes have been done by SPSS version 22. Out of patients, 57 cases were males (54.8%). The male/female ratio was 1.2. The mean age of patients was 6.5 ± 4.3 years. The majority subtypes of patients were M3, M4, non-M3, and M2, respectively. The common molecular abnormalities were t (15;17) and inv (16). Of patients, 19.2% had an early relapse. The mean age of relapse in patients was 6.7 ± 3.9 years. Sixty patients (57.7%) were alive, and 44 cases (42.3%) died during or after therapy. The three years overall survival rate of patients was 42% in this study. According to our data, AML has the same frequency as compared with data from developing countries. But different epidemiological characteristic was a lower rate of three years overall survival in patients. These data may serve the health authorities for more effective environmental and preventive measurements, purposeful allocation of resources for facilitating up-to-date diagnostic and treatment modalities, psychological support programs for respective family members and educational purposes.

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Keywords: Acute myeloblastic leukemia; Malignancy; Survival

Introduction

The major public health issue in worldwide is childhood malignancies that need facilitating specialized centers, medical and nursing personnel and financial resources (1-3). One of the most frequent malignancies in different parts of the world with a prevalence of over 30% of all childhood malignancies is acute leukemia (-6 4). Acute Lymphoblastic Leukemia (ALL) with Acute Myeloblastic Leukemia (AML) implies 97% of acute leukemia (7). Exposure to ionizing agents, certain chemicals, drugs and viruses, genetic defects, and alterations can be causative factors in etiology and pathogenesis of acute leukemia (8), and environmental and socioeconomic conditions are well known predisposing importance (9). As well, recognized risk factors for acute leukemia incidences are cancer history in the family and siblings of children suffering from

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leukemia with a fourfold risk (10-13).

AML is a type of heterogeneous acute leukemia, which is less frequent than ALL (20 versus 80%) and characterized by rapid progression (14-20). The incidence of pediatric AML is 5-7 cases per million annually (21). Childhood AML has a varied incidence rate with a peak in the first two years of life and has a similar frequency in male and female (21-23).

According to official reports, cancer ranks after car accidents and coronary heart disease as the third cause of death in Iran (1) and pediatric cancers rank as the sixth group of common malignancies in Iran (17-19). Literature and reviews show that survival of childhood AML is lower than ALL, and their survival rate has improved during recent decades. In children less than 15 years old, the overall survival rate of AML is between 60-70% (14).

MAHAK Pediatric Cancer Treatment and Research Center (MPCTRC) and Children's Medical Center (CMC) are the main national referral hospitals for childhood malignancies. Due to a large number of referrals to these centers, data compiled can be considered as reference for any issues related to national health strategies and policies to facilitate and optimize medical services for pediatric malignancies.

The purpose of this study was to evaluate the common features of children with AML, who admitted to MPCTRC and CMC for diagnosis and treatment. According to being like a double center study of this manuscript, no investigator could claim about the representativeness of his/her patients to the national pattern.

Materials and Methods

The study group comprised 104 eligible patients with AML, registered at MPCTRC and CMC since April 2007 to April 2011. Patients treated at other centers or referred for consultation were excluded from this study. In the same time span, a total number of eligible and admitted patients with childhood leukemia to MPCTRC and CMC were 545 cases. Diagnosis and treatment of AML were based on clinical manifestations, morphological criteria according to FAB (French-American-British) (14) classification, flow cytometry, and cytogenetic aberrations. Treatment modalities were AML BFM (Berlin-Frankfurt-Munster) - protocol (1983) (14).

Epidemiological Evaluation

A comprehensive questionnaire has been assigned for each patient. It included information about sex, age at diagnosis, immunophenotyping, molecular abnormalities, date of last treatment, date of the last visit, and etc.

Analysis

Data was analyzed by SPSS version 22, with confidence intervals of 95%. Kolmogorov-Smirnov test was used for consideration the distribution of normal or abnormal patterns in variables, *Chi*-square for parametric and Spearman method for non-parametric data, respectively. And also for comparing two means we used t-test.

Results

There were 545 patients with childhood leukemia, who registered at MPCTRC and CMC from April 2007 to April 2011. Out of admitted patients, 441 (80.9%) had acute lymphoblastic leukemia, and 104 (19.1%) had AML. Those 104 eligible patients with AML and less than 15 years old comprised the study group.

Out of enrolled patients, 57 cases were males (54.8%). Patients were categorized according to their age at diagnosis into four groups: <1 year (n=10, 9.6%), 1-5 years (n=36, 34.6%), 5-10 years (n=28, 26.9%), and over 10 years old (n=30, 28.9%). The mean age at diagnosis was 6.5 ± 4.3 years (range 1 month to 15 years). The M/F ratio was 1.2.

The Kolmogorov-Smirnov test has not demonstrated any comparable age distribution pattern in patients. The analysis by Spearman test has not revealed any significant relation between patient's age and sex at diagnosis in the study group.

Out of 104 patients with AML, the majority had M3 (n=21, 20.2%) followed by M4 (n=20, 19.2%), by non-M3 (n=19, 18.3%) and by M2 (n=12, 11.5%). Other types as biphenotype (n=7), M5 (n=6), M1 (n=5), M7 (n=3), M6 (n=2) and M0 (n=1) was reported respectively in considered patients. Unfortunately, 8 cases were as undifferentiated individuals.

Molecular abnormalities were evaluated according to genetic laboratory test's reports. Twenty patients (19.2%) showed positive reports for t(15;17) (n=6, 30%), inversion (n=5, 25%), mosaicism with deletion (n=2, 10%), t(8;21), t(6;11), hyperdiploidy, mosaicism with translocation, mosaicism with monosomy, trisomy 8 and gene deletion (n=1,5%) respectively.

During the treatment,20 cases (19.2%) had an early relapse. The mean age of relapse in patients was 6.7 ± 3.9 years. Chi-square test showed a significant relation

between age and relapse in enrolled patients (*P*-value<0.05).

The last status of patients showed that 60 patients (57.7%) were alive, and 44 cases (42.3%) died during or after therapy. Out of alive individuals, 16 patients (26.7%) were lost to follow-up at MPCTRC and CMC because of referring to other centers for continuing their treatment. The three years overall survival rate of patients was 42% in this study. The mean time of survival was 16 months (Figure 1).

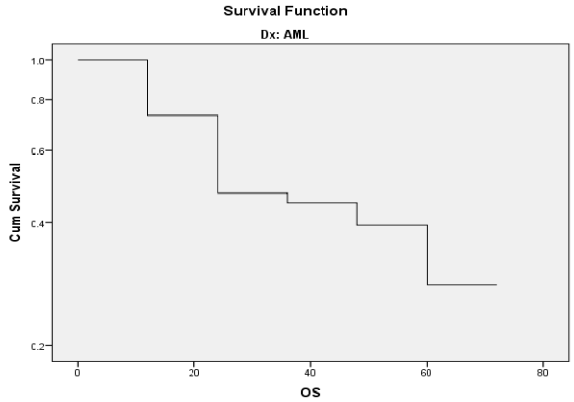

Figure 1. Three years survival rate in enrolled patients

Discussion

AML a type of malignancy affecting the myeloid cell line causes overproduction of abnormal blast cells. The aim of this study was an evaluation of the common features of AML patients, referred and admitted to MPCTRC (MAHAK's Pediatric Cancer Treatment and Research Center) and CMC (Children's Medical Center) for diagnostic procedures, treatment, and follow-up. MAHAK as an NGO to support children suffering from cancer has started since early 1991. It has social and supportive activities in pediatric hematology and oncology departments in academic centers in Tehran. The estimated annual cancer incidence in Iran is 150 per 100.000 in children aged 0-15 years, meaning 3.000-3.500 new cancers, which is higher than reported from developed countries, although some reports indicate an increasing cancer incidence in these countries (19).

The prevalence of acute leukemia in most part of the world is over 30% of all childhood malignancies (2-3). According to MPCTRC and CMC data, ALL comprised 80.9% and AML 19.1% of acute leukemia, which is in concordance with reported reports in the literature (2-8).

The incidence rate of AML in males was higher than females (nearly 1.2 fold) in patients. According to data, in AML group less than five years old the resemblance incidence of sex distribution was revealable. These data has similarity to other literature (3-5, 7-15) . The peak age for enrolled patients being 1-5 years (the mean age=6.5 ± 4.3 years). In this study, the mean age at presentation was similar as reported in the literature (21).

Universal FAB classification in patients with AML reported that types of M5 and M7 are more common in early age groups of children, and other subtypes will see in the elder age groups of patients in this study the patterns of subtypes in enrolled patients were similar to reported reports.

Additional information that obtained from more laboratory techniques regards to genetic make-up of AML cells. Certain cytogenetic changes associated with AML subtypes. Children with AML malignancy have the t (15,17) and inv (16) as the most genetic abnormality in their cell line. In this study, these two molecular abnormalities were more revealed in patients and other genetic disorders were as reported ones in acute leukemia.

Gaynon and coworkers, Azarm and *et al.,* in different studies concluded that nearly 30% of patients with AML encounter with relapse during their treatment. There was a significant relation between sex and age in relapsed AML patients in their findings. In this study, the analysis was in concordance with their findings of relapse in childhood AML.

Overall survival (OS) rates have improved over the past decades in patients with childhood AML. Five years survival rates in children are 55-65% at present. In the current study, the three years survival rate of

patients was 42% as it will decrease for five years survival rate. One of the probabilities of this lower survival rate can be the low number of considered patients as it was only a double center study. For achieving better conclusion through this subject, more evaluation should be considered for patients with childhood AML in Iran.

In conclusion, the presented data demonstrate the same frequency of basically information in patients with childhood AML. However, apart from low overall survival rate in patients, higher male affliction and high mean age at presentation in 1 to 5 years old age group, there are significant differences in terms of subtypes and genetic abnormalities as compared to reports from developed countries (5-6).

By designing advanced projects on patients with childhood acute leukemia, health authorities in other referral childhood centers can utilize epidemiological data compiled at MPCTRC and CMC as the basis for their medical care planning and various informative and educational programs. Furthermore, our data are accessible for academic research institutions.

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