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ORIGINAL ARTICLE

Clinical Features and Induction Outcome of Adult Patients with Acute Lymphoblastic Leukemia: Findings from a Large Tertiary Care Referral Center in Palestine

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Abstract

Objectives: To describe the clinical characteristics and the induction outcome of patients with acute lymphoblastic leukemia (ALL) in adulthood in Palestine.

Methods: A Retrospective single-center study was conducted at An-Najah National University Hospital (NNUH) between January 2014 and December 2018. The files and electronic records of ALL patients were reviewed. All patients at least 15 years or older who were confirmed to have ALL by flow cytometry and started induction chemotherapy at NNUH were included. Descriptive statistics were used.

Results: 43 patients were included; the median age at diagnosis was 23 years, with a male to female ratio of 2.3:1. Most of the patients came from Gaza (37%), Hebron (25.5%), and Nablus (18.6%). The main complaints at presentation were fatigue (60.4%), fever (51.1%), bone pain (41.8%), night sweat (39.5%), anorexia (37.2%), and weight loss (37.2%). Three patients had CNS leukemia, which was 6.9%. The median counts of white blood cells (WBC), hemoglobin (Hb), and platelet counts were 14.4 × 109/L, 9.6 g/dL, and 32 × 109/L respectively. According to flow cytometry reports, B-ALL was the most common subtype, accounting for 60.5%. After one cycle of induction chemotherapy, (83.7%) showed complete remission (CR), (13.9%) did not, and one patient (2.3%) died during the induction period.

Conclusions: The characteristics of ALL patients in Palestine are comparable to published data elsewhere. B-ALL was the most common subtype. The outcome of the first cycle of induction chemotherapy is similar to the published data for both B-ALL and T-ALL subtypes.

Keywords

Acute lymphoblastic leukemia in adults, Clinical features, Flow cytometry, Induction chemotherapy, Palestine

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous group of lymphoid neoplasms that results from monoclonal proliferation and malignant transformation of lymphoid B or T progenitor cells in bone marrow, blood, and extramedullary sites [1]. The clinical presentation of ALL is nonspecific; patients can present symptoms due to blast infiltration of the bone marrow, lymph nodes and other organ infiltration; also they can present with what is known as the "B symptoms", which include fever, weight loss and night sweat [1,2]. ALL demonstrates a bimodal age pattern, with the initial peak incidence around 5 years of age and the second peak around 50 years of age [3]. The diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood [4]. Flow cytometry can be performed to identify lineage-defining antigens and thus determine the ALL subtypes [5]. There are three phases for the treatment of ALL; remission induction, CNS prophylaxis, and maintenance. The duration of treatment ranges from 1.5 to 3 years to eliminate the leukemic cell population [5].

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Leukemia was the fourth most common cancer in Palestine in 2015 (8.5% of all cancer cases) with an incidence rate 7.8 per 100,000 populations [6]. No data available on ALL in Palestine specifically. Updated statistics on the incidence and mortality of ALL in the United States in 2019 are estimated as 5,930 new cases and 1,500 deaths [5].

Since 2014, An-Najah National University Hospital (NNUH) has become the first comprehensive center to treat adults with ALL in Palestine. This study aims to describe the clinical characteristics and the induction outcome of adult ALL patients treated at NNUH. To our knowledge, there are no previous studies addressing this information.

Methods

Study design and settings

This is a single-center retrospective study conducted at NNUH in Nablus, Palestine. NNUH has an active oncology department that accepts on average 800 inpatient admissions each year. It is considered the main referral center for adult leukemia patients from the West Bank and Gaza since January 2014.

Study subjects

All ALL cases admitted to NNUH from January 2014 to December 2018 who were 15 years or older at the time of admission, were confirmed to have ALL by flow cytometry and started induction chemotherapy at NNUH, were included. Patients who discontinued induction chemotherapy or moved to another hospital before finishing induction chemotherapy were excluded.

Data collection

The files and electronic records of ALL patients were reviewed. They include demographic data, detailed history, physical examination, and daily progress notes. The laboratory archives were also reviewed for initial laboratory results, bone marrow biopsy, and flow cytometry results. Data were collected using a pre-designed extraction sheet that included all variables of interest. Information was collected from admission until a confirmed outcome of induction was available. The outcome was confirmed by bone marrow biopsy performed four weeks after initiation of induction chemotherapy. The outcome could be remission (< 5% blasts on bone marrow), non-remission (5% blasts on bone marrow), or death of the patient during the first admission for induction chemotherapy.

Ethical issues

The approval for this research was obtained from the Institutional Review Board (IRB) of An-Najah National University. The extraction sheet for each patient was filled anonymously and the data was coded. The data collected were used for research purposes only.

Statistical analysis

Data were inserted into the Statistical Package for the Social Sciences (IBM-SPSS) statistical software version 23. Analyses of the whole sample were carried out for T-ALL vs. B-ALL subgroups. Data were analyzed using descriptive statistics. Each variable of interest was reported as mean ± standard deviation (SD), median (interquartile range IQR), and percentage.

Results

From January 2014 to December 2018, 58 patients were admitted to NNUH and diagnosed with ALL. Of them, 15 patients were excluded because they did not meet the inclusion criteria. The reports of the remaining 43 patients were reviewed and complete data was extracted. The median age of the patients at diagnosis

Table 1: Demographic data and duration for admission and treatment vs. flow cytometry.

Variable number (%)	**Diagnosis**			
	B-ALL	T-ALL	Burkitt-ALL	Others
Gender 43 (84%)				
Male	17 (65%)	11 (85%)	1 (50%)	1 (50%)
Female	9 (35%)	2 (15%)	1 (50%)	1 (50%)
Age 43 (84%)				
Mean in years (SD)	30.42 (14.5)	24.85 (10)	20 (1.4)	21 (7.1)
Median in years (IQR)	27 (27)	20 (16)	20	21
Duration between first symptom and admission 43 (84%)				
Mean in days (SD)	40.23 (50.7)	27.85 (26.8)	8.5 (2.1)	18.5 (16.3)
Median in days (IQR)	25.5 (50)	14 (38)	8.5	18.5
Duration between admission and start of induction chemotherapy 43 (84%)				
Mean in days (SD)	6.96 (6.3)	5.69 (6.7)	3 (1.4)	4 (1.4)
Median in days (IQR)	6 (3)	3(5)	3	4

Others: Burkitt ALL and Biphenotypic ALL

was 23 years (IQR 17). 30 patients (69.7%) were males, with a male to female ratio of (2.3:1). Regarding geographic distribution, most of the patients were from Gaza (37%), Hebron (25.5%) and Nablus (18.6%), making them the most involved cities. The mean duration between the first complaint and admission to the hospital was 34 ± 42.6 days (see Table 1).

The most common complaints of the patients at the time of presentation were fatigue (60.4%), fever (51.1%), bone pain (41.8%), night sweat (39.5%), anorexia (37.2%) and weight loss (37.2%). Other complaints are summarized in Table 2. Three patients had CNS leukemia accounting for (6.9%) of the sample. At presentation, the median white blood cell count (WBC) was 14.4×10^9/L (IQR 35.2). The median concentration of hemoglobin (Hb) was 9.6 g/dL (IQR 3.4) and the median

Table 2: Initial clinical presentation and lab results vs. flow cytometry.

Variable number (%)	Diagnosis			
	B-ALL	T-ALL	Burkitt-ALL	Others
Symptoms and sings 43 (84%)				
Fatigue	17 (65%)	7 (54%)	1 (50%)	1 (50%)
Fever	14 (54%)	7 (54%)	1 (50%)	0 (0%)
Night sweat	8 (31%)	7 (54%)	1 (50%)	1 (50%)
Bone pain	11 (42%)	5 (38%)	1 (50%)	1 (50%)
Anorexia	8 (31%)	6 (46%)	2 (100%)	0 (0%)
Respiratory tract infection	10 (38%)	4 (31%)	0 (0%)	0 (0%)
Weight loss	11 (42%)	4 (31%)	1 (50%)	0 (0%)
Shortness of breath	8 (31%)	4 (31%)	0 (0%)	0 (0%)
Abdominal pain	3 (12%)	4 (31%)	2 (100%)	1 (50%)
Lymphadenopathy	4 (15%)	5 (38%)	1 (50%)	1 (50%)
Epistaxis	5 (19%)	3 (23%)	2 (100%)	1 (50%)
Pallor	7 (27%)	0 (0%)	0 (0%)	0 (0%)
Headache	8 (31%)	0 (0%)	0 (0%)	0 (0%)
Bruising	5 (19%)	2 (15%)	1 (50%)	0 (0%)
Dizziness	5 (19%)	1 (8%)	0 (0%)	0 (0%)
CNS involvment	2 (8%)	0 (0%)	1 (50%)	0 (0%)
Labs				
WBC count 42(82%)				
Mean × 10^9/L(SD)	22.28 (34.5)	41.71 (43.4)	14.85 (19.3)	39.75 (35.5)
Median × 10^9/L(IQR)	6.3 (28.7)	21.6 (45.7)	14.85	39.75
Hb count 43 (84%)				
Mean g/dl (SD)	9.2 (1.94)	10.8 (2.74)	8.7 (1.84)	10.05 (2.1)
Median g/sd(IQR)	8.9 (3.3)	10.4 (2.4)	8.7	10.05
Platelets count 43 (84%)				
Mean × 10^9/L(SD)	67.98 (79.3)	129.78 (156.2)	23 (4.2)	57.5 (34.6)
Median × 10^9/L(IQR)	31 (85)	48 (271.3)	23	57.5

Others: T-ALL/B-ALL lineage and T-ALL/myeloid lineage; Fever: Temperature > 37.5 orally; Respiratory tract infection: Recurrent upper RTI or lower RTI not responding to conventional treatment; Weight loss: Unintentional documented loss > 5% of total body weight in 6 months; CNS involvement: Based on spinal cytology or documented metastasis on imaging; WBC: White blood cells; Hb: Hemoglobin

Table 3: Outcome of the first cycle of induction chemotherapy vs. flow cytometry.

Variable number (%)	Diagnosis			
	B-ALL	T-ALL	Burkitt-ALL	Others
Outcome 43 (84%)				
Complete remission	22 (85%)	12 (92%)	1 (50%)	1 (50%)
No resmission	3 (12%)	1 (7%)	1 (50%)	1 (50%)
Death	1 (4%)	0	0	0

Others: Burkitt ALL and Biphenotypic ALL

Platelets count was 32 × 10^9/L (IQR 71.5). According to flow cytometry reports, 26 patients (60.4%) have B-ALL, 13 patients (30.2%) have T-ALL, 2 patients (4.6%) have Burkitt ALL, and two patients (4.6%) have Biphenotypic ALL (see Table 2).

Three protocols were used in treatment; Cancer and Leukemia Group B (CALGB), United Kingdom Acute Lymphoblastic Leukemia (UKALL), and Cyclophosphamide, Vincristine, Doxorubicin, and dexamethasone (hyperCVAD) protocol. The mean duration between admission and the start of induction chemotherapy (treatment delay) was 6.2 days. Based on bone marrow biopsy and aspirate results after induction chemotherapy, 36 patients (83.7%) showed complete remission (CR), 6 patients (13.9%) did not show remission, and one patient (2.3%) died during the induction period (Table 3). The cause of death was pulmonary hemorrhage and acute respiratory distress disorder (ARDS) due to DIC.

Discussion

The study describes the clinical characteristics and other characteristics of 43 ALL patients treated at NNUH, which is the main center for the treatment of adult leukemia in Palestine. Therefore, it represents valuable information on the disease status and outcome in Palestine. The median age at diagnosis in our study was 23 years, which is approximately equal to what has been reported by a study from Germany [7], and slightly lower than what reported from Pakistan and Jordan (28 and 33 years, respectively) [8,9]. The median age of the B-ALL patients was higher than that of the T-ALL; 27 compared to 20 years. In our study a male predominance was observed with an M: F ratio of 2.3:1 which was lower than what has been reported in studies from Pakistan (3.4:1) and Iran (4.1:1) [8,10], but higher than what was reported in Jordan (1.7:1) and Germany (1.5:1) [7,9]. Both the B-ALL and T-ALL groups showed male predominance in our study, with the same results seen in China [11].

The most common symptoms our patients had were fatigue (60.4%), fever (51.1%), bone pain (41.8%), night sweat (39.5%), anorexia (37.2%) and weight loss (37.2%). These results were similar to other studies; for example, fever and bleeding were the most common symptoms in Pakistan [8]. Fever, pallor, fatigue, bleeding, and bone pain were the most common in Iranian ALL patients [10].

In this study, spinal cytologically confirmed CNS involvement was present in three of the patients (6.9%), two of them with B-ALL and one with Burkitt-ALL. Similar results were reported from Germany with 6.5% having CNS disease [7], while 10% and 11% of cases had CNS leukemia in Jordan and the United States [9,12].

The mean duration between the first complaint and admission to the hospital (lag time) was 34 ± 42.6 days, which is higher than what has been reported in the United States (mean 16 ± 7.2 days) [13]. The former study concluded that inadequate health insurance is the main cause of delay in diagnosis. The delay in obtaining medical transferences to hospitals and entry permits to the West Bank may be the cause of the lag time in our patients. In our study, this duration was noticed to be shorter in T-All patients (27.8 ± 26.8 days).

At presentation, the median WBC count was 14.4 × 10^9/L, this is slightly higher than what was described in Jordan (9.6 × 10^9/L) [9]. In the B-ALL group, the mean was lower than that of T-ALL; 22.2 × 10^9/L and 41.7 × 10^9/L respectively. Higher numbers were reported from Pakistan, the mean was 69 × 10^9 in the B-ALL group and 82 × 10^9/L in the T-ALL group [8]. The median hemoglobin (Hb) and platelet count at diagnosis were 9.6 g/dL and 32 × 10^9/L, while in Jordan the median was 9 g/dL and 67 × 109/L, respectively [9]. In this study a wide range of hemoglobin counts (5.4-17.3) g/dL and platelet counts (2-472) × 10^9/L counts were found, which could be explained by the fact that some patients had received blood products prior to admission to the hospital.

The most common subtype according to flow cytometry reports was B-ALL (60.4%). Similar results were reported from Egypt, Pakistan, Iran and Sweden; with B-ALL accounts for 74.5%, 70%, 87.8% and 82% of their patients respectively [8,10,14]. The T-ALL was the second most common accounting for (30.2%) of our cases, which is comparable to what was reported from Egypt, Pakistan, and Iran [8,10,14].

Regarding the outcome, 83.7% showed complete remission (CR) after a single cycle of induction chemotherapy; this is similar or slightly better to what Shaikh, et al. (2011), Mashhadi, et al. (2012), Koslowski, et al. (2017), and Abbasi, et al. (2013) reported in their studies (85%, 77.3%, 83%, 88% respectively). Only one case died before finishing induction chemotherapy, after 13 days of admission. The remission rates for B-ALL and T-ALL were 84.6% and 92.3%, respectively.

Strengths and Limitations

This is the first study on the clinical features of adult ALL patients in Palestine. So, it represents a strong foundation for further studies on this disease. It also compares the outcome of our patients in NNUH with other centers worldwide. NNUH became the first comprehensive center to treat adults with ALL and receive patients from all over Palestine. The small sample size has precluded the use of inferential statistics. The retrospective nature of the study and the dependence on medical records and archive could decrease the accuracy of the data, although we reviewed every piece of information carefully.

Conclusions

Our study describes the clinical characteristics and induction outcome of ALL patients in Palestine. The

induction results of ALL patients in Palestine are similar data published elsewhere. The success of therapy for adult patients with ALL highlights the importance of central patient referral to academic facilities and adherence to international protocols.

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