INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a clonal hematological disease characterized by inadequate normal hematopoiesis secondary to excessive proliferation of leukemic blasts and their impaired differentiation. As a result, patients usually manifested symptoms related to bone marrow failure. It's very uncommon for ALL patients to present with normal hemogram ***(Chen et al., 2010).***

ALL is the predominant leukemia of childhood that runs an aggressive course and causes death within a few months if untreated ***(Neville et al., 2009)***.

The incidence of ALL in adults is relatively low. The aetiology of most leukemia is uncertain. Although they are thought to be caused by a combination of environmental and genetic factor ***(Buffler et al., 2005).***

Osteopathy is not an uncommon initial manifestation of ALL. In a pediatric population, radiological abnormalities in the musculoskeletal system were demonstrated in about 40% of ALL patients ***(Sinigaglia et al., 2008).***

In contrast, skeletal morbidity is relatively rare in adult ALL. Because of its low incidence, the reported clinical experience of adult ALL with skeletal morbidity is rather limited, and the outlook for adult patients is still not conclusive ***(Hu et al., 2012).***

Bone pain, resulting from either bone erosion, periosteal lesions, or massive proliferation of blasts in the medullary canal and under the periosteum, is one of the most common presenting symptoms of ALL. In patients with ALL, who presented with prominent skeletal symptoms, they tended to have no lymphoadenopathy, organomegaly, or leukocytosis ***(Chen et al., 2010).***

Childhood acute lymphoplastic leukemia (ALL) is the most common childhood leukemia type, in which overall survival (OS) at 5 years is more than 80% ***(Pui et al., 2008).*** Contrary to childhood ALL, the incidence of ALL in adult is lower and the prognosis is worse. Over the past decades, some therapeutic progress in adult ALL has been achieved with an average OS of 35%, which mainly rely on tailored therapeutic strategies according to the advances of prognostic factors and risk stratification ***(Bassan et al., 2011)***.

Skeletal morbidity itself is an independent poor prognostic factor for OS and EFS. Patients with skeletal morbidity may be an independent disease entity with further investigation. A better understanding of the pathophysiology of ALL patients with skeletal morbidity and more intensive therapeutic strategies are needed for these patients ***(Hu et al., 2012).***

AIM OF THE WORK

The aim of this study is to assess bone mineral density in young adult patients with (ALL) at presentation and after induction of therapy.

ACUTE LYMPHOBLASTIC LEUKEMIA

Definition:

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease characterized by the accumulation and proliferation of clonal lymphoid progenitor cells in the bone marrow, periphery and / or extramedullary sites ***(Michael et al., 2012)***. As a consequence there is accumulation of an immature B- or T- cell clone in the bone marrow resulting in the suppression of normal hematopoiesis and in various extramedullary sites.80-85% of ALL are of B-cell lineage (B-cell precursor ALL "BCP-ALL"), and 15-20% are of T-cell lineage (T-ALL) **(*Graux, 2011).***

Epidemiology:

Incidence:

The estimated annual incidence of adult acute lymphoblastic leukemia (ALL) is about one in 100, 000**(*Renato and Dieter*, 2011)**.In 2012 in the United States, approximately 6050 new cases were diagnosed, accounting for 1440 deaths (for adults and children) ***(Siegel et al., 2012)***. Men and Caucasians have a slightly higher risk than women and African Americans ***(Mackenzie and Kasner, 2012).***

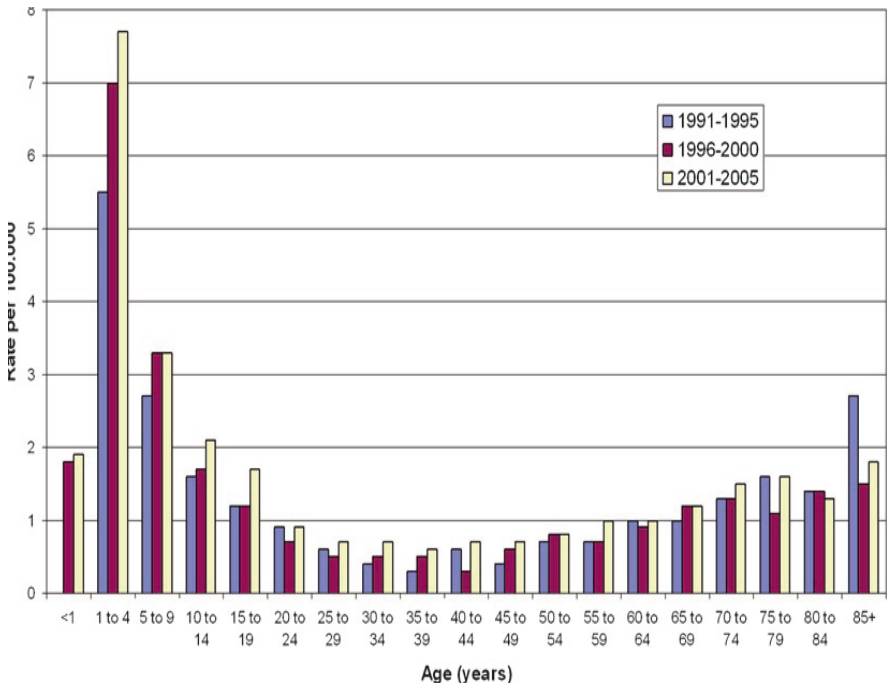

Fig. (1): Age-specific incidence rates for acute lymphoblastic leukemia by observation period. Data based on Surveillance, Epidemiology, and End Results (SEER) Program Cancer Statistics Review ***(Reis et al., 2008).***

Age differences:

ALL exhibits a bimodal age distribution with an early peak between ages 2-5 years (4-5 per 100, 000 individuals, accounting for 80% of all childhood leukaemia), followed by a second peak after the age of 50 years ***(Joanne et al., 2012).***

Survival:

The survival of younger patients with acute leukemia has improved in the early 21st century, but it is unknown whether people of all ethnic and racial backgrounds have benefited

equally. Overall, the 5-year survival increased from 31.6% in 1997-2002 to 39.0% in 2003-2008 for patients with acute lymphoblastic leukemia ***(diaane et al., 2013).*** In contrast to children, in whom the rate of cure approaches 90%, less than half of adults attain disease eradication, even with hematopoietic stem cell transplantation (HSCT***) (Hillard and Anjali, 2012).***

Mortality:

The 5- year death rate in the most recent Children, s Oncology Group (COG) cohort was 25% for 15-to 19-year-olds ***(Archie et al., 2012).***The age-adjusted death rate for all ALL cases in the USA was 0.5 per 100, 000 people for the period 2001–2005 ***(Reis et al., 2008).***

Aetiology:

The aetiology of most leukaemia is uncertain. Although they are thought to be caused by a combination of environmental and genetic factors ***(Chung et al., 2011).***

(1) Genetic Factors:

Certain inherited syndromes seem to carry an increased risk of developing ALL including Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia telangiectasia, and neurofibromatosis. Leukemia-specific fusion genes and gene rearrangements have been identified in the neonatal period in patients who subsequently developed ALL

(Mackenzie and Kasner, 2012). In addition, exposure in utero to ionizing radiation, pesticides, and solvents has also been related to an increased risk for childhood leukemia ***(Onciu, 2009).***

(2) Physical and Chemical Factors:

Other factors for which the evidence is weak or lacking include: residential or occupational nuclear exposure to child or father, non-ionizing radiation, pesticides, benzene, cigarette smoke, vitamin K, cod liver oil, natural alcohol use, dietary nitrates (hot dogs), and drinking water contaminated with trichloroethylene (***Redaelli et al., 2005).***

(3) Viruses:

Other factors such as infections have been reported as etiologies in the pathogenesis of ALL. Associations of human T-cell lymphotrophic virus type 1 (HTLV-1) with adult T-cell leukemia/lymphoma, of Epstein-Barr virus with mature B-cell ALL, and of human immunodeficiency virus (HIV) with lympho-proliferative disorders have been described. Associations with varicella and influenza viruses have been suggested ***(Jabbour et al., 2005).***

Presentation:

The clinical presentation of acute lymphocytic leukemia (ALL) may range from insidious nonspecific symptoms to sever acute life-threatening manifestations, reflecting the extent of

bone marrow involvement and degree of extramedullary spread. In younger patients anemia-induced fatigue may be the only presenting feature. Dyspnea, angina, dizziness, and lethargy may reflect the degree of anemia in older patients presenting with ALL. Approximately half of all patients may present with fever attributable to the pyrogenic cytokines, such as IL-1, IL-6, TNF, released from the leukemic cells, infection, or both. Arthralgia and bone pain due to the bone marrow expansion by the leukemic cells and occasionally necrosis can be observed, although less commonly in adults compared to children. Pallor, petechiae, and ecchymosis in the skin and mucous membranes due to thrombocytopenia, DIC, or a combination of the above may be observed. ALL may present with either leukopenia (~20%) or moderate (50%–5–25×10^9/L) and severe leukocytosis (10%–>100 ×10^9/L). Neutropenia is common. The majority of patients present with platelet counts less than 100 × 10^9/L (75%), while 15% have platelet counts of less than 10 × 10^9/L. Patients with ALL (particularly T-ALL), may present with symptoms of cough, dyspnea, stridor, or dysphagia from tracheal and esophageal compression by a mediastinal mass (15% of patients). Compression of the great vessels by a bulky mediastinal mass also may lead to the life-threatening superior vena cava syndrome. In addition to the above mentioned symptoms, patient may develop cyanosis, facial edema, increased intracranial pressure, and syncope ***(Olga et al., 2011)***.

Central nervous system involvement at presentation can be associated with altered mental status and neurologic deficits. Splenomegaly and lymphadenopathy are common. Extramedullary involvement with involvement of the testis, retina or skin has been reported ***(Narayanan and Shami, 2011).***

Diagnosis:

Initial work-up starts by a complete history, physical examination and laboratory evaluation. Besides morphologic evaluation, cytogenetic analysis, immuno-phenotyping and molecular diagnostics are required to confirm the diagnosis and for risk stratification ***(Narayanan and Shami, 2011).***

(A)-Laboratory Diagnosis:

1- CBC, peripheral blood counts regularly show anaemia and thrombocytopenia, but might show leucopenia. A normal leucocyte count, or leukocytosis based on the number of circulating malignant cells. So are not diagnostic of leukaemia. The diagnosis of ALL is usually made by bone marrow biopsy ***(Chung et al., 2011).***

2- Bone marrow, although peripheral blasts with anemia and thrombocytopenia are strongly suggestive of ALL, the definitive diagnosis of ALL is based on the bone marrow aspiration or biopsy demonstrating more than 20% lymphoblasts ***(Esparza and Sakamoto, 2005)***.

3- Other laboratory findings: include elevated serum lactate dehydrogenase, increased uric acid, elevated creatinine, disruptions of calcium and phosphate metabolism, and decreased levels of circulating immunoglobulins ***(Redaelli et al., 2005).***

4- Radiology: radiological studies include chest X-ray, computed tomography(CT)scan and/or abdominal/pelvic ultrasound, MRI, Tc 99-seintigraphy and PET-scaning, are essential **(*Sirelkhatim et al., 2009).***

5- Lumbar puncture: To evaluate for the presence of CNS involvement, a lumbar puncture (LP) is typically performed on patients with ALL. The presence of at least 5 leukocytes per mL of CSF (with leukemic blasts apparent in the sample) or the presence of cranial nerve palsies defines CNS leukemia ***(Olga et al., 2011).***

Staging of ALL is performed at the time of diagnosis and must be done by using morphological, immunological, and genetic methods. These three methods are useful for first diagnosing a haemopoietic malignancy, then for determining the subtype of leukaemia, and finally for establishing the specific type of ALL ***(Redaelli et al., 2005).***

(B)-Pathologic Diagnosis:

1-Morphologic evaluation:

The French-American-British (FAB) classification system separates ALL cases into three groups based on the morphological characteristics of the tumour cells ***(Redaelli et al., 2005).*** FAB classification outlined three morphologic groups of ALL, designated as L1, L2, And L3. Most commonly, ALL blasts are small to intermediate in size, with Scanty cytoplasm, condensed nuclear chromatin, and indistinct or absent nucleoli (FAB L1 subtype). Less commonly, ALL cells may be larger, with moderate amounts Of pale basophilic cytoplasm, finely dispersed nuclear chromatin, and prominent Nucleoli (FAB L2 subtype).Very rarely, ALL may present as the FAB L3 subtype, which Consists of large blasts, with abundant deeply basophilic and occasional vacuolated cytoplasm, coarsely clumped nuclear chromatin, and variably prominent nucleoli. Most of the cases presenting with this morphology are Burkitt lymphomas, a subtype Of high-grade mature B-cell lymphoma.However, a small subset of precursor B-cell neoplasms, often associated with hypodiploidy, may also present with FAB L3 features ***(Onciu, 2009).***

The FAB classification has been replaced by the World Health Organization (WHO) classification. In the latter, ALL

was divided into precursor B-cell, precursor T-cell and Burkitt-cell leukemia. The WHO classification has been recently revised. In this revision, Burkitt-cell leukemia has been eliminated and is now considered a leukemic phase of Burkitt's lymphoma. ALL is now divided into B lymphoblastic leukemia/lymphoma, not otherwise specified; B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities; and T lymphoblastic leukemia/lymphoma (Table 1). The distinction between leukemia and lymphoma is based mainly on bone marrow involvement by the disease. The finding of 20% or more leukemic blasts in the bone marrow is consistent with a diagnosis of leukemia ***(Narayanan and Shami, 2011).***

The most recent WHO classification (2008) recognizes several specific entities among patients with B-cell ALL, defined by the presence of particular chromosomal abnormalities associated with unique phenotypic and prognostic features (Table 1). They include t(9; 22), t(v; 11q23), t(12; 21).

B-ALL with hyperdiploidy, B-ALL with hypodiploidy, t(5; 14), and t(1; 19). Other chromosomal abnormalities, such as del(6q), del(9p), and del(12p) do not appear to impact the outcome of ALL patients ***(Olga et al., 2011).***

Table (1): WHO classifcation of ALL (Olga et al., 2011).

Precursor B lymphoblastic leukemia/lymphoma not otherwise specified (NOS)
Precursor B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
t(9; 22) (q34; q11.2); BCR-ABL1
t(v; 11q23); MLL rearranged
t(12; 21) (p13; q22); TEL/AML 1 (ETV6-RUNX1)
B-ALL with hyperdiploidy
B-ALL with hypodiploidy
t(5; 14) (q31; q32); IL3-IGH
t(1; 19)(q23; p13.3); E2A-PBX1(TCF-PBX1) Precursor T-cell acute lymphoblastic leukemia

Among patients with T-ALL the most common recurrent cytogenetic translocations involve the α and δ TCR loci at 14q11.2, the β locus at 7q35, and the γ locus at 7p14–15 with a variety of partner genes ***(Han et al., 2007).*** In most cases, these translocations lead to an inappropriate activation of *structurally intact* transcription factor proto-oncogenes such as HOX11(TLX1) (10q24), HOX11L2 (TLX3) (5q35), MYC (8q24.1), TAL1 (1p32), RBTN1 (LMO1) (11p15), RBTN2 (LMO2) (11p13), LYL1 (19p13) and LCK (cytoplasmic

tyrosine kinase) (1p34.3–35). Some translocations result in a creation of *fusion genes*, such as PICALM-MLLT10 t(10; 11) (p13; q14) and MLL-ENL t(11; 19) (q23; p13). Activating mutations in the NOTCH1 gene, important for T cell development, are detected in 50% of adult T-ALL patients and are associated with a shorter survival ***(Graux et al., 2006).***

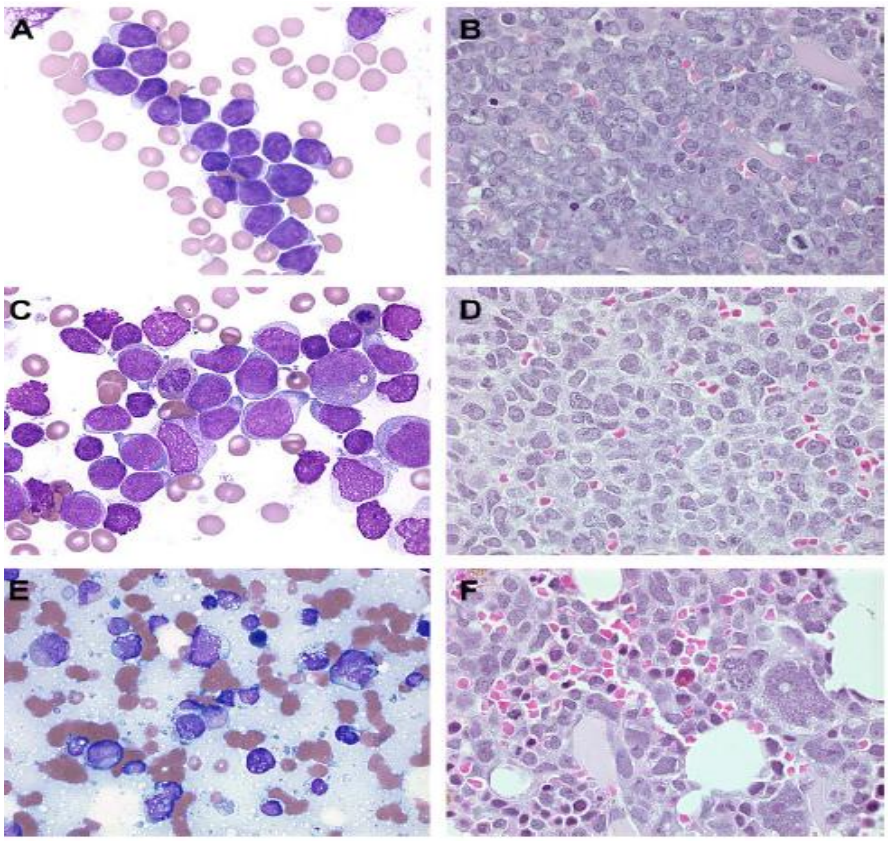

Fig. (2): The morphology of ALL/LBL in smears and paraffin-embedded tissue sections. (A, B) ALL L1. (C–D) ALL L2. (E, F) Morphologic findings in a case of precursor B-ALL with hypodiploidy, resembling a high-grade, mature B-cell lymphoma (A, C, E, Wright-Giemsa stain) (B, D, F, hematoxylin-eosin; original magnification 60x oil immersion) ***(Onciu, 2009).***

2-Cytochemistry:

Cytochemical staining has been used with decreasing frequency in the diagnosis of ALL due to the availability of Immunophenotyping.The leukemic cells of ALL are uniformly negative for myeloperoxidase (MPO), Sudan Black-B, chloroacetate esterase, and non specific esterases. The blasts of ALL are often (75%) positive for PAS and may also be positive for acid phosphatase, more frequently seen in T-cell ALL ***(Onciu, 2009).***

3-Immunophenotypic assessment:

Essential in the work-up of patients with ALL. Immunophenotyping by flow cytometry became a preferred method of lineage assessment due to its ease of application in clinical settings and to its ability to analyze multiple antigens simultaneously on each cell. Immunohistochemical stains on bone marrow biopsy sections can be performed as an alternative since a wide variety of antibodies to both lymphoid- and myeloid-associated antigens reactive in paraffin-embedded sections are now available. Most leukocyte antigens lack specificity; hence, a panel of antibodies is required to establish the diagnosis and to distinguish among the different immunologic subtypes of leukemic cells.The lymphoblasts in B-ALL are almost always positive for the B-cell markers: CD19, cytoplasmic CD79a, and cytoplasmic CD22. None of these markers by itself are specific