Patterns of relapse in adult Acute lymphoblastic leukemia

(Retrospective study)

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List of Abbreviations

ALL: Acute Lymphoblastic Leukemia

BMT: Bone marrow transplantation

CD: Cluster of Differentiation

CNS: Central Nervous system

CR: Complete remission

CR1: first complete remission

CR2: second complete remission

CSF: Cerebrospinal fluid

DFS: Disease-free survival

IPT: Immunophenotyping

IT: Intrathecal

MTX: Methotrexate

MRD: Minimal residual disease

NEMROCK: Kasr EL-Eini Center of Radiation Oncology and nuclear medicine

OAS: Overall Survival

PH+: Philadelphia chromosome

SCT: Stem cell transplantation

t: Translocation

TLC: Total Leucocytic count

SE: Standard error

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Abstract

Although ALL is a rare disease yet it has a disproportionately large effect on cancer survival **(Haskel et al, 1995).**

This study was based on retrospective analysis of the data of 40 adult patients with ALL who presented to NEMROCK in the period from 2000 to 2010. Follow up period extended till the end of December 2011, with analysis of response and survival in relation to different risk factors.

During the period 2000-2010, two treatment protocols; Holzer and unit C protocols were used. The overall initial response was 82.5%. Comparing the two groups, CR rate was 87.5 Vs 96.1%, and relapse rate was 71% Vs 26% for the two protocols respectively. Systemic relapse represented 69% of all relapses, followed by CNS relapse which represented 31% of relapsed cases.The 5 years overall survival was 57.8%.

Keyword : laymphoblastic-cancer-leukemia-diagnosis of relapse

Introduction & Aim of work

Acute lymphoblastic leukemia (ALL) is biologically and clinically a heterogenous group of diseases characterized by clonal expansion and arrest at a specific stage of normal lymphoid haemopoesis **(casciato et al, 2000).**

Although ALL is a rare disease yet it has a disproportionately large effect on cancer survival **(Haskel et al, 1995)**.

There has been significant progress in treating adult ALL over the past two decades and currently 60-80% of patients will achieve a complete remission following combination chemotherapy induction and 30-40% will become long-term survivors and possibly cured**. (Pui CH & Roberson LL, 2008).**

The development of cytogenetic and molecular tests can now better define prognostic groups allowing for individualized treatment regimens for patients with high- and low-risk features. **(Pui CH & Roberson LL,2008).**

Out of 15865 cancer pateints seen at NEMORCK in the period from 1995 to 2003, adult ALL constitutes 0.31 % of total number **(Haggag,FA, 2003).**

The long term disease free survival in adult ALL is approximately 40% after aggressive post remission chemotherapy .

(Zhang, MJ & Hoezler D, 2010).

Relapse in ALL is usually systemic constituting 50-70% of relapse patterns. Isolated CNS relapse occurs in 3-10 % of adult ALL according to different risk factors **(Cataland& Lareson 2003).**

Without CNS prophylaxis, CNS recurrence occurs in approximately 30-50% of patients. Although it is generally understood that the outcome of adults with ALL, who develop CNS recurrence is dismal, no studies have detailed the results of such patients, consequently, the management of adults with ALL and CNS recurrence has not been standardized, and little progress has been made in this area**. (Fiere D & Lepage E et al, 2001).**

Testicular relapse is extremely rare in adults. In pediatric ALL particularly T-cell subtype, testicular involvement was once a common problem .Overt testicular involvement by leukemia at diagnosis occur in approximately 2% of male with ALL. With modern chemotherapy, especially the use of intermediate to high dose MTX, this is now rare. **(Edward C & Halperin, 2008).**

Objectives and Aim of work

The aim of this work is to study the pattern of relapse in adult ALL cases presented to NEMROCK from Jan. 2000- Dec. 2010.

The available data were used to evaluate the efficacy of the treatment protocols which have been used in this period.

According to the results, the treatment protocols &/or the method of CNS prophylaxis can be modified.

Chapter 1

Epidemiology

Incidence

Acute lymphoblas c leukaemia represents 12% of all leukaemia cases childhood and adults, with a worldwide incidence projected to be 1 to 4.75 per 100,000 people. Italy, the United States (US), Switzerland, and Costa Rica are the countries with the highest incidence of ALL. Hereditary link, genetic defects, and possibly radiation or chemical exposures are listed amongst the most significant risk factors.

Acute lymphoblastic leukaemia is predominantly a disease of childhood, but it affects adults as well; it is relatively high through teens, falls during the next two decades and increases steadily beyond 45 years of age. The incidence is slightly higher in men than in women**. (Annino et al,2002)**

Complete remission rates are high, especially amongst children; however, long-term survival at 10 years is in the range of 63% for children and 25-35% for adults. This implies that there is s ll a strong need for new therapies to maintain remission and prolong survival. **(Redaelli A, et al 2005)**

In Egypt, there is no available registration as regard overall incidence of ALL in relation to other types of cancer every year; but it can be estimated from data published by National Cancer Program of Egypt in different governorates. ALL represented 2.3% of all cancer cases in Aswan 2008 registry, 1.8% in Damie a 2009 & 1.5% in Minya 2009**. (NCRPE, 2011).**

Etiology:

Till now, we do not know the cause of most cases of acute lymphocytic leukemia (ALL). A genetic predisposition to ALL can be deduced from a higher incidence of ALL among mono- and dizygotic twins of ALL patients, but some cases can be linked to certain *risk factors*. There are only a few known risk factors for ALL.

Radiation exposure

A high level of radiation exposure is a risk factor for both types of acute leukemia. People who survived the atomic bomb in Japan had a much higher risk of ge ng acute leukemia, usually within 6 to 8 years.

The risk of leukemia from lower levels of radiation, such as from radiation treatment, x-rays, or CT scans, is not well-known. It is also not clear how much the exposure of a fetus to radiation within the first months of development might increase the risk of leukemia. *(***Pieters R, et al, 2010)**

Chemicals

The risk of ALL may be increased by exposure to certain chemicals like benzene and certain chemotherapy drugs. Chemical exposure is more strongly linked to an increased risk of AML than to ALL. **(Rushton L, 1997)**

Viral infections

Infectious etiologies are implicated in the pathogenesis of ALL. Associations have been described with HTLV-1 as the e ologic agent of adult T cell leukemia/lymphoma (ATLL) **(Mahieux R, 2003),** and Epstein-Barr virus (EBV) with mature B-cell ALL and HIV-related lymphoproliferative disorders **(Lombardi L, 1987).**

Genetic contribution:

A-Identical twin with ALL

Having an identical twin with ALL is a risk factor for ALL. This risk is mostly in the first year of life. Many doctors feel this increased risk may be due to leukemia cells being passed from one fetus to the other while still intra uterine. (**De Oliveira MSP, 1986**)

B-Inherited syndromes:

ALL does not appear to be an inherited disease. It does not seem to run in families, so a person's risk is not increased if a family member has the disease. But there are some inherited syndromes that seem to raise the risk of ALL. These include:

Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiectasia and Neurofibromatosis**. (Mertens AC, 1998**)

Recent studies have implicated a protective effect of a polymorphism in the methylene-tetrahydrofolate reductase (MTHFR) gene in infant and adult ALL, pointing toward genetic susceptibility genes as part of ALL etiology**.**

(Wiemels JL, 2001)

Chapter2

Molecular biology of adult ALL

Classification :

ALL has been classified by 3 different ways: Morphologic, Immunologic and Cytogenetic.

1-Morphologic:

The French American British (FAB) Cooperative Group distinguishes three ALL groups (L1 to L3) based on morphologic criteria (cell size, cytoplasm, nucleoli, basophilia, and vacuolation)

Whereas the morphologic dis nc on between L1 and L2 has lost its prognos c significance, L3 morphology is associated with mature Bcell ALL (Burkitt's lymphoma) and is characterized by a high rate of cell turnover giving rise to the "starry sky" pattern on marrow biopsies. **(Benne JM, et al, 1976)**

ALL blasts are negative for myeloperoxidase (MPO) although low-level MPO posi vity (3 to 5%) may occur in rare cases that otherwise lack expression of myeloid markers by flow cytometry (**Serrano J, et al. 1997)**

Terminal deoxynucleotidyl transferase (TdT), albeit not specific for ALL, remains a useful marker to separate malignant lymphocytosis from reactive processes, and to dis nguish L3 ALL (TdTnegative) from other ALL subtypes **(Huh YO, 2000)**

2-immunologic:

Immunophenotyping by flow cytometry has become an essential part of ALL diagnosis. Three broad groups can be distinguished: precursor B-cell, mature B-cell, and T-cell ALL (Table1).

Table(1): Immunophenotypic Classification of Acute Lymphoblastic Leukemia

B Lineage		**T Lineage**	
CD19/CD79a/CD22		**CD3 (surface/cytoplasmic)**	
Pre-pre-B ALL	—	Precursor T ALL	CD1a, CD2, CD5, CD7, CD8, cCD3
Common ALL	CD10 (CALLA)	Mature T ALL	Surface CD3 (plus any other T-cell markers)
Pre-B ALL	Cytoplasmic IgM		
Mature B-cell ALL	Cytoplasmic or surface Ig		

(Huh YO,et al, 2000).

Precursor B ALL blasts are positive for TdT, HLA-DR, CD19, and CD79a. Different stages of maturation have been defined as pre-pre-B ALL (pro-B-ALL), common ALL, and pre-B ALL. Whereas pre-pre-B ALL blasts are positive for CD19, CD79a, or CD22, but no other B-cell differentiation antigens, common ALL (cALL, early pre-B-ALL) is characterized by expression of CD10 (common ALL antigen, CALLA), and pre-B-ALL by expression of cytoplasmic immunoglobulins with or without CD10. Mature B-cell ALL (Burkitt's

lymphoma) blasts are positive for surface immunoglobulins (sIg, usually IgM), are clonal for kappa or lambda light chains, and are negative for TdT. Similarly to B-lineage ALL, T ALL can be further stratified into subtypes based on different stages of intrathymic differentiation **(Onciu M, et al. 2002)**

Surface CD3 (sCD3) is the most lineage-specific marker for T-cell differentiation and is typically positive in mature T ALL. Mature T ALL is also positive for either CD4 or CD8 but not both. Blasts in pre-T-ALL are nega ve for sCD3, but may s ll express cytoplasmic CD3**(Gores SD, 1991)**

Pre-T-ALL is nega ve for both CD4 and CD8. CD52 is expressed in about 30 to 50% of cases of T ALL. It is not lineage-specific, but may have therapeutic significance when using the anti-CD52 monoclonal an body Alemtuzumab.

Coexpression of markers from more than one lineage can be demonstrated in 15 to 50% in adult ALL and 5 to 35% in children**.**

(Pui CH, 1998)

Using flow cytometry, lineage can be assigned in more than 95% of cases and truly biphenotypic leukemias are rare. **(Preti HA et al, 1995).**

3- Cytogenetic:

Recurrent cytogenetic and molecular abnormalities are common in adult ALL (Table 2) (**Mancini M, et al. 2005)**. They not only have prognostic significance, but also provide insights into the molecular events underlying the leukemic phenotype.

Differences in the frequency with which good- and poor-prognosis karyotypes occur in childhood versus adult ALL exist and may partly explain differences in outcome among children and adults. More recently, oligonucleotide or cDNA microarray technologies are being investigated to