ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA AN EGYPTIAN EXPERIENCE

Thesis

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This work is dedicated to my parents and my husband for their help and prayers

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Abstract

Acute lymphoblastic leukemia has a relatively poor prognosis in adults with long-term survival only 30–40% of newly diagnosed individuals. High risk disease defining includes advanced age, very elevated WBC at presentation, the presence of adverse cytogenetic changes (eg; Ph chromosome +ve) and Pro-B cell ALL immunophenotype. As outcome in high-risk disease is significantly worse than for standard risk disease. Adult ALL remains a challenging disease. While the only treatment that results in long-term DFS in patients with ALL in CR2 is allogeneic HSCT and outcomes from transplantation are better if performed in CR1 rather than CR2.

In this retrospective study, fifty-five adult patients with ALL were submitted and followed up after allogeneic bone marrow transplantation from HLA identical sibling donor during the period between April 1997, and June 2006. Twenty eight of them presented initially with high-risk disease and underwent an allo-BMT in first CR. The remaining twenty seven patients were those who relapsed after attaining first CR and were transplanted in second CR. We evaluate both groups regarding the transplant related mortality (TRM), disease free survival (DFS) , the overall survival (OS) and correlation between OS and age, gender, graft versus host disease (GVHD), CD34+ cells dose and also the correlation between GVHD and CR, gender, pre-transplant virology of the recipient and conditioning regimen with comparing the whole results to the international one.

In our study TRM (100 day mortality) was (32.2%) in CR1 and (51.9%) in CR2. OS at one year was (64.2%) in CR1 and (51.85%) in CR2. While tow years OS was (46.4%) for CR1 and (48.1%) for CR2. DFS was (46.4%) in CR1 and (40.7%) in CR2 at one year. And it was (25%) and (33%) for CR1 and CR2 at tow years respectively. OS was higher in patients who developed chronic GVHD with significant P value (P=**0.05**).The incidence of development of chronic GVHD was higher in CR1 than in CR2 with significant P value (**P=0.006**). While the increase in the age of patients was significant factor in development of acute GVHD with P value (P=0.05). Also incidence of acute GVHD was high in patients with HBs Ag +ve (P= **0.03)**.

In conclusion: The incidence of chronic GVHD was higher in CR1 than in CR2 with significant P value (P=0.006). older age was found to be a significant factor in development of acute GVHD with P value (P=0.05). In addition, incidence of acute GVHD was high in patients with HBs Ag +ve (P= 0.03).

Key words: bone marrow transplantation-acute lymphoblastic leukemia-peripheral stem cell transplant.

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List of abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ANA	Alpha naphthyl acetate
ANB	Alpha naphthyl butyrate
APL	Acute promyelocytic leukemia
ATG	Anti-Thymocyte globulin
Bcr/Abl	Breakpoint cluster region/ Abelson murine leukemia virus
BM	Bone marrow
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BW	Body weight
CALGB	Cancer and Leukemia Group B
CFU-GM	Colony-forming unit granulocytemacrophage
CIBMTR	Center for International Blood and Marrow Transplant Research
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CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete remission
CSA	Cyclosporine-A
CSF	Cerebrospinal fluid
CY	Cyclophosphamide
DFS	Disease- free survival
DLI	Donor lymphocyte infusion
EBMT	European Group for Blood and Marrow Transplantation
EBV	Epstein–Barr virus
ECOG	The Eastern Cooperative Oncology Group
EFS	Event-free survival
EORTC	European Organization for Research and Treatment of Cancer
FAB	French–American–British
FISH	Fluorescent insitu hybridization
FLU	Fludarabine
G-CSF	Granulocyte colony-stimulating factor

GMALL	German Multicenter ALL Cooperative Group
GM-CSF	Granulocyte macrophage colony- stimulating factor
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
GVM	Graft-versus-malignancy
HLA	Human Leucocytic Antigen
HSCT	Hematopoietic stem cell transplantation
IBMTR	The International Bone Marrow Transplant Registry
IG	Immunoglobulin
IT	Intra-thecal
MDS	Myelodysplastic syndrome
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
MNC	Mononuclear cell
MPO	Myeloperoxidase
MRC	Medical Research Center
MRD	Minimal Residual Disease
MTX	Methotrexate
NaF	Sodium Fluoride
NHL	Non-Hodgkin's lymphoma
NMA	Nonmyeloablative
NMDP	the National Marrow Donor Program
NSE	Nonspecific esterases
OS	Over All survival
PAS	Periodic acid-Schiff
PBSC	Peripheral blood stem cells
PCP	Pneumocystitis Carenii
PCR	Polymerase chain reaction
Ph+	Philadelphia chromosome
SBB	Sudan black B
TBI	Total-body irradiation
TCR	T-cell receptor
TdT	Terminal deoxynucleotidyl transferase
TRM	Transplant related mortality
UCB	Umbilical cord blood
URD	Un Related Doner
WBC	Wight Blood Count
WHO	World Health Organization

ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULTS

DEFINITION

Acute lymphoblastic leukemia is a neoplastic disease that results from somatic mutation in a single lymphoid progenitor cell at one of several discrete stages of development. The immunophenotype of the leukemic cells at diagnosis reflects the level of differentiation achieved by the dominant clone (1).

HISTORICAL BACKGROUND

Only a few decades ago, acute lymphoblastic leukemia (ALL) was an incurable disease in all but a small minority of patients. Progress in the treatment of pediatric ALL has been substantial. This is clearly illustrated in the results reported from a series of successive clinical protocols from St. Jude Children's Research Hospital (2). The initial clinical trials from 1962 to 1969 introduced multiagent chemotherapy regimens into pediatric ALL therapy. This proved superior to single agent therapy, but, still few children experienced long-term survival.

The next era, from 1967 to 1979, saw effective prevention of leukemia relapse in sanctuary sites in the Central nervous system (CNS) using cranial irradiation and intrathecal (IT) chemotherapy. Intensification of postremission therapy with administration of non–cross-resistant drugs was responsible for improving survival in subsequent cohorts. With further refinements, as well as general improvement in supportive care, approximately 85% of children with ALL are now cured of the disease.

The success demonstrated in the pediatric ALL trials led to similar approaches in the treatment of adults. Outcomes in consecutive cohorts of adults with ALL treated by a collaborative study group gradually improved as treatment was intensified and extended. Compared with the success in treating childhood ALL, however, the degree of improvement is only modest (3).

INCIDENCE

ALL represents about 12 % of all leukemias diagnosed in the United States, and 60 % of all cases occur in persons younger than 20 years (4). ALL is the most common malignancy diagnosed in patients under the age of 15 years, accounting for one-fourth of all cancers and 76 % of all leukemias in this age group (5).

A peak between the ages of 2 and 5 years, followed by falling rates during later childhood, adolescence, and young adulthood (4), characterizes age-specific incidence patterns.The incidence rates raise again, beginning in the sixth decade and reaching a second, smaller peak in the elderly. The incidence of ALL in blacks is approximately one-half the incidence rate in whites. There is a slight male predominance with a male to female ratio of 1.3:1.0.Geographic differences in the incidence of ALL are reflected by higher rates in North America and Europe and lower rates in African and Asian populations (6).

ETIOLOGY AND PATHOGENESIS

The initiation and progression of ALL is driven by successive mutations that differ according to the developmental stages of the affected blast cells. Thus, specific subtypes of ALL appear to have genetically distinct origins linked to different causative mechanisms. The cause of ALL is essentially unknown, and few clues can be derived from epidemiologic studies. Environmental agents, such as ionizing radiation and chemical mutagens, have been implicated in the induction of ALL in some patients. However, the vast majority of cases lack discernible etiologic factors. The favored concept is that leukemogenesis reflects the interaction between multiple genetic and environmental factors, a model that needs to be confirmed in well-designed population and molecular epidemiologic studies (7).

Inherited factors and genetic predisposition syndromes are more relevant to childhood ALL. Survivors of the nuclear fallout from the atomic bombing in Hiroshima and Nagasaki have an overall relative risk of 9.1 for ALL, greater among those exposed in childhood, with the peak incidence occurring 6 to 7 years after radiation exposure (8). Somewhat more relevant to adult ALL is the association between occupational exposure to low-dose ionizing radiation among nuclear workers in the United States and Europe and a slightly increased risk for leukemia, although findings were inconsistent across populations (9). Among chemical environmental exposure, high-level benzene exposure that occurred before contemporary occupational standards is generally accepted as a cause of bone marrow aplasia, chromosome damage, and leukemia (10).

Cigarette smoking was linked to a small increase in risk for ALL among persons older than 60 years in one report (11). Secondary acute leukemias occurring after exposure to chemotherapeutic agents are usually myeloid, although rare cases of therapy-related ALL have been observed (12).

RISK FACTORS

Despite the paucity of knowledge of factors that increase the risk of ALL, a minority (5%) of cases are associated with inherited, predisposing genetic syndromes, often involving genes whose encoded proteins affect genomic stability and DNA repair (13). A variety of normal inherited genetic polymorphisms may also contribute indirectly to the risk of leukemia, for example, those involving enzymes important in carcinogen metabolism and detoxification and those affecting the regulation of immune responses (14).

GENETIC SYNDROMES

Children with Down syndrome have a 10- to 30-fold increased risk of leukemia. Acute megakaryoblastic leukemia predominates in patients younger than 3 years and ALL in older age groups. Down syndrome cases are more likely to have B-cell precursor ALL, and their leukemic cells lack adverse genetic abnormalities (15).

Autosomal recessive genetic diseases associated with increased chromosomal fragility and a predisposition to ALL include ataxia-telangiectasia, Nijmegen breakage syndrome, and Bloom syndrome .The lymphocytes and leukemic cells of patients with ataxia-telangiectasia frequently have chromosomal rearrangements involving bands 7p13-p14, 7q32-q35, and 14q11 (sites of the T-cell receptor gamma, beta, and alpha/delta genes respectively), as well as band 14q32 (site of the immunoglobulin heavy-chain gene). The mutation of ataxia-telangiectasia patients may allow a large increase in production of translocations at the time of V (D) J recombination, leading to an increased predisposition to ALL (16).

Patients with other constitutional or acquired immunodeficiency diseases, such as congenital X-linked agammaglobulinemia, immunoglobulin A deficiency, and variable immunodeficiency, are also at increased risk for this disease (17).

Although impaired immune surveillance contributes to the increased risk of Epstein-Barr-virus-related malignancies in patients with acquired immunodeficiency, there is no compelling evidence that defective immunity contributes to the predisposition to ALL in patients with ataxia-telangiectasia or other congenital immunodeficiency syndromes.

FAMILIAL LEUKEMIA

Reports of two or more leukemia cases in the same family are rare, reinforcing the notion that heredity plays only a minor role in the causation of this disease. Even so, fraternal twins and siblings of affected children have a twofold to fourfold greater risk of developing leukemia than do unrelated children during the first decade of life. When leukemia occurs in one identical twin, the other twin has a 20 % chance of developing the disease (18). If leukemia develops in the index twin before the age of 1 year, the other twin almost invariably will develop leukemia, typically within a few months. Molecular studies have demonstrated that intrauterine metastasis from one twin to the other via their shared placental circulation is responsible for the concordant leukemia (19).

ENVIRONMENTAL FACTORS

In utero (but not postnatal) exposure to diagnostic X-rays confers a slightly increased risk for the development of ALL, which correlates positively with the number of exposures (20). The evidence for an association between the development of ALL and nuclear fall out, occupational, cosmic ionizing radiation exposure or paternal preconception radiation exposure is weak. Nonionizing radiation in the form of low-energy electromagnetic fields produced by residential power supply and appliances is not a factor in the development of childhood ALL according to a recent comprehensive study (21).

Molecular Pathogenesis

Molecular abnormalities can be grouped according to the functional consequence of oncogenic mutation. Acquired constitutive activation of the ABL protein kinase by rearrangement with the BCR gene is an example of a mutation that confers a proliferative advantage (22). The fusion gene is the consequence of the t(9;22)(q34;q11) balanced chromosomal translocation, which is the most common cytogenetic abnormality in adult ALL. ABL is a nonreceptor tyrosine protein kinase that enzymatically transfers phosphate molecules to substrate proteins, thereby activating downstream signal transduction pathways important in regulating cell growth and proliferation (23). Other gene rearrangements result in loss- or gain-of-function mutations involving transcription factors that are important for normal hematopoietic development (24). An example is the t(12;21)(p13;q22) chromosomal translocation, which juxtaposes the TEL and AML1 genes (25). Excluding numerical aberrations, TEL- AML1 is the most frequent cytogenetic abnormality in childhood ALL, although it is uncommon in adults.

Another general mechanism of cancer formation involves loss or inactivation of tumour-suppressor genes, many of which have key regulatory functions in controlling cell cycle progression (26). Examples are p16 (INK4A) and p15 (INK4B). Stock et al. investigated the incidence of cell cycle regulatory gene abnormalities in adult patients with de novo ALL treated by the Cancer and Leukemia Group B (CALGB) study group (27). Deletions, micro deletions, and gene rearrangements involving p16 (INK4A) and p16 (INK4B) were common occurrences.
Even more frequent was aberrant expression of Rb and p53, two other tumour–suppressor genes. Concurrent abnormalities involving two or more of these genes were found in one-third of adult ALL patients.

CLINICAL FEATURES

SYMPTOMS:

The clinical presentation of ALL is variable. Symptoms may appear insidiously or acutely. The presenting features generally reflect the degree of marrow failure and the extent of extramedullary spread. Approximately half the patients present with fever, which often is induced by pyrogenic cytokines released from the leukemic cells, including interleukin-1, interleukin-6, and tumor necrosis factor.In about a third of the patients, fever results from infection. Regardless of its origin, fever in leukemia patients resolves within 72 h after the start of induction therapy (28).

Fatigue and lethargy are frequent manifestations of anemia in patients with ALL. In the older patient population, anemia-related dyspnea, angina, and dizziness may be the dominant presenting features (29).
One-third has bleeding symptoms at diagnosis, which is less frequent than in patients presenting with acute myeloid leukemia. Severe hemorrhage is uncommon (30).

The patients may present with a limp, bone pain, arthralgia, owing to leukemic infiltration of the bone, or joint or to expansion of the marrow cavity by leukemic cells. In a small proportion of patients, marrow necrosis can result in severe bone pain and tenderness, fever, and a very high serum lactate dehydrogenase level. However, bone necrosis is less common in adult than in children (31). Arthralgia and bone pain are less severe in adult patients.

Less common signs and symptoms include headache, vomiting, alteration of mental function, oliguria, and anuria. Occasional patients present with a life-threatening infection or bleeding (e.g., intracranial hematoma).