Disease Outcome of Newly Diagnosed Pediatric Acute Myeloid Leukemia Patients treated at Children Cancer Hospital, Egypt.

THESIS

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List of Abbreviations

ADCC	Antibody Dependent Cellular-Mediated Cytotoxicity
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
AMKL	Acute Megakaryocytic Leukemia
AML1/ETO	Acute Myeloid Leukemia 1/Eight Twenty One
AMML	Acute Myelomonocytic Leukemia
AMoL	Acute Monoblastic Leukemia
APL	Acute Promyelocytic Leukemia
AR	Allelic Ratio
ATRA	All-Trans Retinoic Acid
BAALC	Brain And Acute Leukemia, Cytoplasmic
BFM	Berlin- Frankfurt-Muenster
CALGB	Cancer And Leukemia Group B
CBFB	Core Binding Factor Beta
CCG	Children's Cancer Group
CCHE	Children Cancer Hospital Of Egypt
CD	Cluster Determinants

CEBP-α	Ccaat/Enhancer Binding Protein Alpha
CNS	Central Nervous System
COG	Children's Oncology Group
CR	Complete Remission
CSF	Cerebro-Spinal Fluid
DFCI	Dana-Farber Cancer Institute
DFS	Disease-Free Survival
DLI	Donor Leukocyte Infusion
EFS	Event-Free Survival
FAB	French-American-British
FISH	Fluorescence In Situ Hybridization
FLT3	FMS-Like Tyrosine Kinase 3
G-CSF	Granulocyte Colony-Stimulating Factor
GVHD	Graft-Versus-Host Disease
GVL	Graft Versus Leukemia
HCT	Hematopoietic Cell Transplantation
HDT	High Dose Therapy
HLA-DR	Class Ii Human Leukocyte Antigens

HSPC	Hematopoietic Stem/Progenitor Cells
ITD	Internal Tandem Duplications
JMML	Juvenile Myelomonocytic Leukemia
KD	Kinase Domain
LSC	Leukemia Stem Cells
MDR 1	Multidrug Resistance Gene 1
MDS	Myelodysplastic Syndrome
MLL	Myeloid/Lymphoid, Or Mixed-Lineage, Leukemia
MPD	Myelo-Proliferative Disease
MPO	Myeloperoxidase
MRC	Medical Research Council
MRD	Minimal Residual Disease
MYH11	Smooth Muscle Myosin Heavy Chain 11
NASDA	Naphthyl-Asd-Chloroacetate Esterase
NF-1	Neurofibromatosis Tumor Suppressor Gene
NHL	Non-Hodgkin Lymphoma
NPM	Nucleophosmin
NSE	Nonspecific Esterase

PAS	Periodic Acid-Schiff
PML/RAR-	Pro-Myelocytic Leukemia / Retinoic Acid Receptor Alpha
POG	Pediatric Oncology Group
PR	Partial Remission
RBC	Red Blood Corpuscle
RTKs	Receptor Tyrosine Kinases
RT-PCR	Reverse Transcription- Polymerase Chain Reaction
SBB	Sudan Black B
SCT	Stem Cell Transplant
SIRS	Systemic Inflammatory Response Syndrome
SJCRH	St. Jude Children's Research Hospital
TKI	Tyrosine Kinase Inhibitors
TLC	Total Leukocytic Count
URD SCT	Unrelated Donor Stem Cell Transplantation
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization
WT-1	Wilms Tumor Suppressor Gene

ABSTRACT

Key words: Acute Myeloid Leukemia - Pediatrics– Risk Factors for Relapse.

Acute myeloid leukemia comprises a fascinating group of hematologic disorders that arise within bone marrow precursors of the myeloid, monocyte, erythroid, and megakaryocytic cell lineages. Over the past few years, our understanding of the pathogenesis of AML has shown that different subgroups of AML require different, risk-adapted treatment strategies. Eighty-three (83) previously untreated patients who presented to the Children Cancer Hospital of Egypt with the diagnosis of AML during the period from July 2007 to December 2008 were included in this retrospective study aiming at identifying relapse risk group parameters, especially during periods of clinical remission and illustrating the most common causes of early and late deaths. All biologic and epidemiologic data of the included patients were collected such as; age, gender, initial white cell count, as well as some biologic markers that may affect response to therapy, reflecting on remission and survival rates. Patients were followed for a period ranging from 2 – 18.5 months, 40 patients (58.82%) were still alive in complete remission, 4 patients (5.88%) were alive but relapsed, 9 patients (13.24%) died in complete remission, and 6 patients (8.82%) died in relapse. Only 3 patients underwent hematopoietic stem cell transplantation and all of them were still alive in CR till study date. Early deaths were seen in 15 patients (18.07%), mainly due to bleeding and leukostasis. Late deaths were seen in 23 patients (27.71 %), mainly due to progressive disease, sepsis and fungal chest infections. Analysis of our study data revealed statistically significant association of MLL rearrangements and complex karyotypes with increased risk of relapse (P = 0.017 and 0.007 respectively). On the other hand it didn't reveal such an association of gender, initial TLC > 100 $X10^9$/L, initial CSF infiltration with blasts, nor FLT3/ITD positivity with increased risk of relapse. The association of t(8;21) and inv.16 with complete remission status was not of statistical significance, yet it approached statistical significance. (P = 0.064)

Introduction and Aim of Work

INTRODUCTION

Acute myeloid leukemia (AML) comprises a fascinating group of hematologic disorders that arise within bone marrow precursors of the myeloid, monocyte, erythroid, and megakaryocytic cell lineages. ***(Hope KJ, 2004)*** Over the past few years, our understanding of the pathogenesis of AML has shown that different subgroups of AML require different, risk-adapted treatment strategies.

In 2001, the World Health Organization (WHO), in conjunction with the Society for Hematopathology and the European Association of Hematopathology, published a new classification for myeloid neoplasms. A number of chromosomal abnormalities are used to predict outcome and stratify therapeutic risk groups in children with AML. ***(Warner, et al. 2004)***

With recent innovations in diagnosis, treatment and follow-up, prognosis of childhood AML has improved significantly over the past decades, from nearly no child surviving to a present probability of cure of approximately 60%. However, this can only be achieved using very intensive chemotherapy which results in relatively high rates of treatment related deaths and significant late effects. ***(Arceci, et al. 2002)***

Although attempts to increase the intensity of induction have not significantly improved CR rates, there is evidence that induction intensity improves ultimate outcome. ***(Woods, et al. 1996)***

Since the mid-1970s, many AML trials have examined the effects of the duration and intensity of post-remission therapy on outcome. Despite the different strategies employed by these trials, outcome results were similar. ***(Arnaout, et al. 2000)***

Better understanding of the molecular pathogenesis of AML has led to the development of target-specific therapies. Some of the new classes of drugs include monoclonal antibody directed against the CD33 antigen, farnesyl-transferase inhibitors (FTI), and FMS-like tyrosine kinase 3 (FLT3) inhibitors. ***(Ruffner, et al. 2000)***

The role of allogenic SCT, particularly whether it should be done during first CR or reserved for second remission, remains the most controversial issue in pediatric AML. ***(Linker CA, et al. 2000)***

Furthermore, the morbidity and mortality associated with currently used chemotherapy regimens significantly limit overall success. A growing number of studies have documented an increasing number of treatment-related late effects for patients with cancer. ***(Leung W, et al. 2000)***

A major challenge for the future will be to overcome drug resistance of the leukemic blasts while reducing the short- and long-term adverse side effects of treatment. An improved understanding of the molecular heterogeneity of AML should provide important clues to successfully meeting this challenge.

AIM OF WORK

This is a retrospective study including previously untreated patients presented to the Children Cancer Hospital of Egypt with the diagnosis of AML during the period from July 2007 to December 2008, aiming at;

- Exploring the epidemiologic data of de novo pediatric acute myeloid leukemia (AML) patients at the Children Cancer Hospital of Egypt.
- Assessment of the prognostic value of biological markers in childhood AML.
- Identifying the relapse risk group parameters based on cytogenetic abnormalities and early response to therapy.
- Demonstration of the most common causes of early and late deaths among patients of acute myeloid leukemia.

Review of Literature