A 5-year retrospective study of treatment outcome in acute myeloid leukemia (AML) patients

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Abstract

Introduction & Aim of Work:

This is a retrospective observational study aiming at evaluation of response, and relapse rates as well as survival outcome of acute myeloid leukemia (AML) patients treated at our institute.

Patients & Methods:

The study included 117 AML patients presented to Kasr Al Ainy Center of Radiation Oncology and Nuclear Medicine (NEMROCK) during the period from January 2010 to December 2014.

We reviewed patients' files for clinical and pathological characteristics as well as details of treatment and response. Patients diagnosed as acute promyelocytic leukemia (APL) were identified and analyzed separately.

Results:

Ninety non-APL patients were included in the study, having mean age of 37.8 years and slight female predominance (male: female ratio 1:1.3). The most common French-American-British (FAB) subtypes were M2 and M5 representing 22% and 21% of patients, respectively.

Complete remission (CR) rate was 65%, 13.8% of patients were refractory to treatment and early mortality rate was 12.5%. Half of the patients in remission eventually relapsed, and a second remission (CR2) was achieved by 31.6% of patients who received salvage therapy. The estimated overall survival of 90 AML patients was 11.5 months (95% CI: 6 – 17). Overall mortality rate was 53.3%, majorly of resistance to therapy (primary refractory and relapsed disease).

It has been shown that hyperleukocytosis imposed poor response to chemotherapy and short overall survival in our study. Of clinical characteristics, poor performance status was the prominent factor affecting overall survival. Interruption of treatment during induction therapy impaired response rate, while incomplete consolidation treatment impaired both disease free- and overall survival outcomes.

Twenty seven APL patients were identified in our cohort, constituting 23% of AML patients at our institute. The mean age was 35 years, and male: female ratio was 1:1.25. The majority of patients (44%) were of intermediate risk Sanz score, and 30% were high risk.

CR was achieved by 63% of patients, and 3.7% had persistent refractory disease. No deaths were encountered before starting treatment, and early mortality rate was 14.8%. By the end of consolidation cycles, molecular CR was achieved by 82.4% of patients.

Relapse rate was 29.4%, and CR2 was achieved by 75% of patients who received salvage therapy. The median disease free survival of our patients was 27.1 months, the mean overall survival was 84.4 months, and the median OS was not reached. Overall mortality rate in APL was 26%, mainly due to treatment complications.

The highest survival outcomes were noted in normal body mass index patients. Omission of anthracyclines and treatment interruption during induction significantly hampered overall survival of our patients. Moreover, insufficient consolidation treatment impaired overall survival, while shortened maintenance duration impaired disease free survival.

Conclusion:

Resistance to therapy represents a daunting challenge and a major cause of mortality in our patients. This reflects the need for risk-adapted treatment strategies and optimal supportive care in an attempt to improve survival outcomes.

Keywords:

Acute myeloid leukemia - acute promyelocytic leukemia - NEMROCK - Egypt - treatment - survival - mortality.

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List of Abbreviations

- 2-HG: 2-hydroxyglutarate
- ALFA: Acute Leukemia French Association
- ALL: Acute Lymphoblastic Leukemia
- Allo-SCT: allogeneic stem cell transplantation
- AMegL: Acute Megakaryocytic Leukemia
- AML: Acute Myeloid Leukemia
- AML-im: immature AML
- AML-ma: mature AML
- APL: Acute Promyelocytic Leukemia
- ATO: Arsenic Trioxide
- ATRA: All-trans Retinoic Acid
- AUL: acute undifferentiated leukemia
- AYA: Adolescents and Young Adults
- BMDSCs: Bone Marrow-derived Stromal Cells
- CBF β: Core-binding Factor Subunit β
- CBF: Core-binding Factor
- CBF-AML: Core-binding factor AML
- CEBPA: CCAAT/enhancer binding protein α
- CEBPAdm: CCAAT/enhancer binding protein α double mutation
- CEBPAsm: CCAAT/enhancer binding protein α single mutation
- CHD4: Chromodomain Helicase DNA-binding Protein 4
- CLL: Chronic Lymphocytic Leukemia
- CMML: Chronic Myelomonocytic Leukemia
- CN-AML: cytogenetically normal AML
- CNAs: Copy Number Alterations
- CNS: Central Nervous System

- COG: Children's Oncology Group
- CpG: Cytosine-guanine sequences
- CR: Complete Remission
- CRP: C-reactive protein
- CSF: cerebrospinal fluid
- D5-PBCR: Day 5 peripheral blast clearance rate
- DCE-MRI: Dynamic contrast-enhanced magnetic resonance imaging
- DFS: Disease free survival
- DIC: Disseminated Intravascular Coagulation
- $DNMT3A^{MUT}$: DNMT3A mutations
- DS: Down Syndrome
- DS-AML: Acute Myeloid Leukemia of Down syndrome
- DSB: Double-stranded break
- DVT: Deep Vein Thrombosis
- EFS: Event free survival
- ELN: European LeukemiaNet
- EMD: Extramedullary disease
- EML: Extramedullary Leukemia
- EMR: Early mortality rate
- EORTC: European Organisation for Research and Treatment of Cancer
- EPI: European Prognostic Index
- ERG: Erythroblast transformation specific-related gene
- EVI1: Ecotropic Viral Integration Site 1
- FAB: French-American-British
- FISH: Fluorescence in-situ hybridization
- FLT3/ITD: Tyrosine kinase internal tandem duplication
- Gas6: Arrest-specific Gen
- GEOCAP: The Geolocalisation des Cancers Pediatriques
- GIMEMA: Gruppo Italiano Malattie Ematologiche dell' Adulto
- GO: Gemtuzumab ozogamicin
- GOELAMS: Groupe Ouest Est d'Etude des Leucemies et Autres Maladies du Sang
- HCT: Hematopoietic cell transplantation
- HDAC: high-dose cytarabine
- HSCs: Hematopoietic Stem Cells
- IDH1: Isocitrate dehydrogenase 1
- JALSG: Japan Adult Leukemia Study Group

- LDH: Lactate Dehydrogenase
- lncRNs: Long non-coding RNAs
- LOH: Loss of Heterozygosity
- LSC: Leukemia Stem Cell
- MDA: MD Anderson
- MDS: Myelodysplastic Syndrome
- MFC: Multiparameter flow cytometry
- MITO: Mitoxantrone
- MLL: Mixed-lineage leukemia
- MLL5: Mixed lineage leukemia 5
- MPAL: Mixed phenotype acute leukemia
- MPN: Myeloproliferative Neoplasia
- MPO: myeloperoxidase
- MRC: Medical Research Council
- MRD: Minimal residual disease
- mRNA: messenger RNA
- MS: Myeloid Sarcoma
- MVD: Microvessel density
- NCRI: UK National Cancer Research Institute
- NK: Normal Karyotype
- NOS: Not otherwise specified
- NPM1: Nucleophosmin
- NPMc+ AML: AML with cytoplasmic NPM
- OS: Overall Survival
- PA-AML: Pregnancy-associated acute myeloid leukemia
- PARP1: Poly(ADP-ribose) polymerase 1
- RAEB: Refractory anemia with excess blasts
- RAEB-t: RAEB in transformation
- RARA: Retinoic Acid Receptor Alpha
- RDS: Respiratory Distress Syndrome
- RFS: Relapse-free survival
- RIL-2: recombinant interleukin-2
- RT-PCR: Reverse-transcriptase polymerase chain reaction
- RUNX: Runt-related Transcription Factor
- s-AML: Secondary AML
- SCT: Stem Cell Transplantation
- SD-DN: Standard-dose daunorubicin

- SEER: Survival, Epidemiology, and End Results
- SNP: single nucleotide polymorphism
- SWOG: Southwest Oncology Group
- TAM: Tyro3, Axl, Mer
- t-AML: Therapy-related AML
- TDT: Time from diagnosis to treatment
- TET: Ten-Eleven Translocation
- TKD: Tyrosine kinase domain
- TL: Transient Leukemia
- TLC: Total leukocyte count
- TLS/FUS: Translocated in sarcoma/fused in sarcoma
- TRM: Treatment-related Mortality
- VEGFA: Vascular Endothelial Growth Factor A
- WBC: White blood cell
- WHO: World Health Organization
- WT1: Wilms Tumor-1
- α-KG: α-ketoglutarate
- β2-MG: β2 microglobulin

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Introduction and Aim of Work

Acute myeloid leukemia (AML) is one of the challenging hematological malignancies worldwide. Several advances have been made in the diagnostic utilities and treatment options in the past few years, urging risk-adapted therapy for these cases.

In adults, AML is the commonest type of leukemia with a pattern of male predominance, and a steep rise of incidence with advancing age. Compared with all other subtypes, 5-year relative survival is the highest for acute promyelocytic leukemia (APL) patients **(Dores G.M., et al., 2012).**

Survival over the past two decades has increased among AML patients due to incorporation of intensive and potentially curative treatment over time, including bone marrow transplantation for eligible patients **(Dinmohamed A. G., et al., 2014).**

Several clinical situations still represent a daunting challenge in the management of AML patients, posing a high risk of increased morbidity and mortality. Hyperleukocytosis dramatically increases early mortality rate due to leukostasis, respiratory distress syndrome, or disseminated intravascular coagulation **(Troitskaya V. V., et al., 2014).**

In acute promyelocytic leukemia patients, hemorrhagic complications remain the most frequent cause of mortality. Thus, prompt diagnosis and recognition of any coagulation defect is imperative at presentation **(Breen K.A., et al., 2012).**

This retrospective observational study aims at analyzing patients' characteristics, different treatment regimens, and survival outcome of AML patients who presented to Kasr Al Ainy Center of Radiation Oncology and Nuclear Medicine (NEMROCK) during the period from January 2010 to December 2014.

Rates of remission and relapse, as well as causes of treatment failure and mortality are investigated, in an attempt to modify treatment strategies and improve outcome of AML patients treated at our institute.

Chapter (1)
Epidemiology and Pathogenesis of Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is a morphologically and genetically heterogeneous disease characterized by malignant clonal proliferation of immature myeloid cells in the bone marrow, peripheral blood, and occasionally other body tissues. This process results in inhibition of normal hematopoiesis, leading to neutropenia, anemia, thrombocytopenia, and the clinical features of bone marrow failure.

Epidemiology:

Nearly 91% of leukemia patients are diagnosed at age 20 years and older. Acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) are the most common types diagnosed in adults, whereas acute lymphoblastic leukemia (ALL) is most common among children and adolescents. In AML patients, median age at diagnosis is 67 years. **(DeSantis C.E., et al., 2014).**

In adults, AML is the commonest type of leukemia accounting for about 25% of all leukemias. Pediatric disease accounts for about 7% of AML cases and its biology is somewhat distinct from that of adults, with a significantly lower incidence of aggressive, high-risk disease **(Dores G.M., et al., 2012).**

There are approximate 18,800 new cases diagnosed with AML each year in the United States alone, but estimated death is as high as 10000, ranking AML as the 6^{th} highest cancer-related death in male population **(Zhou J., et al., 2014).**

In Egypt, leukemia comprises 10% of all malignancies, with AML representing 16.9% **(Egypt Cancer Registry, 2011).**

Leukemia (all forms) is expected to affect 1% of females and 1.5% of males during their lifetime, and is the leading cause of cancer death in males younger than 40 years and in females younger than 20 years. AML is much more common in older people, with a continuous slow rise in young adulthood turning into a rapidly increasing incidence by age from approximately 50 years. The peak incidence