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Clinical Outcomes for Patients with Acute Myeloid Leukemia harboring IDH1 mutation after Intensive Chemotherapy

Thesis

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List of Abbreviations

Abb.	Full term
2HGD.....	2-hydroxyglutarate dehydrogenases
AML.....	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
ASXL1	Additional sex comb-like 1 mutations
ATO	Arsenic trioxide
ATRA.....	All-trans retinoic acid
CBFA2	Core-binding factor subunit-2
CBFB	Core binding factor beta subunit
CD	Common differentiation
CEBPA....	Ccaat enhancer binding protein
CIBMTR .	Center of international blood and marrow transplant research
CN-AML.	Cytogenetically normal
CR	Complete remission
DFS	Disease free survival
DIC.....	Disseminated intravascular coagulation
DNMT3A	Dna methyltansferase 3a mutations
ELN.....	European leukemianet
EVI1.....	Ecotropic virus integration site 1
FAB.....	French-american- british classification
FLT3	Fms-like tyrosine kinase 3 mutations
HLADR...	Human leukocyte antigen-antigen d related
HMAs.....	Hypomethylating agents
HRM	High resolution melt

HSCT	Hematopoietic stem cell transplantation
IDHs.....	Isocitrate dehydrogenases
ITD.....	Internal tandem duplications
JAK2	The janus kinase 2 gene
JM	Juxta-membrane
L-2HG	L-2-hydroxyglutarate enantiomer
MDS.....	Myelodysplastic syndrome
MLL	Mixed lineage leukemia
MPD.....	Myeloid proliferative disorder
MPL	Myeloproliferative leukemia
MRD	Minimal residual leukemia
MYH11 ...	Smooth muscle myosin heavy chain 11
NADPH...	Nicotinamide adenine dinucleotide phosphate
NGS.....	Next generation sequencing
NPM1.....	Nucleophosmin 1
OS	Overall survival
PCR.....	Polymerase chain reaction
PHDs.....	Prolyl hydroxylases
PML-RARA	Promyelocytic leukemia/retinoic acid receptor alpha
PTD.....	Partial in tandem duplications
RUNX1 ...	Runt-related transcription factor
RUNX1T1	Runx1 partner transcriptional co-repressor 1
SRSF2	Serine/ arginine-rich- splicing-factor-2 gene
t-AML	Therapy-related aml
TdT.....	Terminal deoxynucleotidyl transferase

- TET2 ..... Ten–eleven translocation 2
- TKD ..... Tyrosine kinase domain
- TKI..... Tyrosine kinase inhibitors
- UK NCRC United kingdom national cancer research institute
- WT1 ..... Wilms‘ tumor 1 gene
- α-KG ..... A-ketoglutarate

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INTRODUCTION

Acute myeloid leukemia (AML) is heterogeneous myeloid disorder with multifactorial pathogenic mechanisms and a broad range of prognosis. AML is characterized by clonal proliferation of poorly differentiated cells of the myeloid lineage ***(Dohner et al., 2015).***

The pathogenesis involve recurrent genomic alterations, including somatic gene mutations and/or chromosomal abnormalities, that can define biologically distinct clinical subtypes ***(Vardiman et al., 2009).***

Comprehensive genomic profiling at the time of diagnosis can inform disease classification, risk stratification and prognosis and ultimately allow for more selective therapeutic interventions. Alterations to cellular metabolism, as well as somatic mutations of genes essential to epigenetic regulation, are implicated in the pathogenesis of several human malignancies***(Cairns et al., 2011; Conway et al., 2014).***

Isocitrate dehydrogenases (IDHs) are homodimeric enzymes involved in diverse cellular processes, including adaptation to hypoxia, histone demethylation and DNA modification***(Clark et al., 2016).***

IDH1 protein catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) to produce reduced nicotinamide adenine dinucleotide phosphate.

Diverse dioxygenases depend on sufficient levels of α-KG for multiple cellular processes, as well as for epigenetic regulation ***(Molenaar et al., 2014).***

IDH1 enzymes are localized to the cytoplasm and peroxisomes ***(Clark et al., 2016).***

Somatic mutations in IDH1 (mIDH1) genes have been described in both solid and hematological malignancies ***(Stein, 2016).***

IDH1mutations are heterozygous, retaining one wild-type, suggestive of an oncogenic gain of function. IDH proteins are encoded by the IDH1 gene located at chromosome 2q33. Recurrent IDH1 mutations are missense variants leading to a single amino-acid substitution of arginine residues at codon 132 in exon 4 of the IDH1 gene. Additionally, a germline-synonymous single-nucleotide polymorphism (rs11554137) located in codon 105 in exon 4 of the IDH1 gene has been reported to have prognostic relevance in AML***(Willander et al., 2014; Wagner et al., 2010).***In our study we will provide an overview of the Clinical Outcomes for Patients with Acute Myeloid Leukemia Harboring IDH1 mutation after Intensive Chemotherapy.

Aim of the Work

The aim of the present study is to detect IDH1 Mutation in adult Egyptian AML patient and find correlation between the mutation and prognosis & survival in those patients after intensive chemotherapy.

Chapter (1)
Acute Myeloid Leukemia

I. Introduction

Acute myeloid leukemia (AML) is a heterogeneous disorder characterized by clonal expansion of myeloid progenitors (blasts) in the bone marrow and peripheral blood. Previously incurable, AML is now cured in approximately 35%-40% of patients younger than age 60 years old. For those >60 years old, the prognosis is improving but remains grim. Studies have revealed that the disorder arises from a series of recurrent hematopoietic stem cell genetic alterations accumulated with age. Using deep sequencing techniques on primary and relapsed tumors, a phenomenon called clonal evolution has been characterized with both founding clones and novel subclones, impacting the therapeutic approach. Despite an increased understanding of AML biology, our efforts to this point in changing treatment strategy have been disappointing. In this review, we discuss the current diagnostic and prognostic strategies, current treatment approaches and novel therapies critical to AML management ***(Khwaja et al., 2016).***

II. Morphology

Morphologically, AML blasts vary in size from slightly larger than lymphocytes to the size of monocytes or larger. The nuclei are large in size, varied in shape and usually contain several nucleoli. AML blasts express