Role of XPD and XRCC1 DNA Repair Genes Single Nucleotide Polymorphisms in the Pathogenesis and Outcome of Acute Myeloid Leukemia

(Thesis)

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List of contents

List of abbreviations

• ALL	Acute lymphoblastic leukemia.
• AML	Acute myeloblastic leukemia
• AP site	AP endonuclease 1
• APE1	Apurinic/apyrimidinic site
• ASCT	Autologous stem cell transplant
• AT	Ataxia telangiectasia syndrome
• BAALC	Brain and acute leukemia cytoplasmic
• BARD1	BRCA1-associated–RING-domain 1 protein
• BER	Base excision repair
• BRCA1	Breast cancer type 1 susceptibility protein
• BRCA2	Breast cancer type 2 susceptibility protein
• BRCT	BRCA1 C-terminus
• BM	Bone marrow
• cdks	Cyclin-dependent kinases
• CEBPA	CCAAT/enhance binding protein alpha
• CHK1	Checkpoint kinase 1
• CHK2	Checkpoint kinase 2
• CML	Chronic myelogenous leukemia
• COG	Children's Oncology Group
• CR	Complete Remission
• CYP	Cytochrome P450
• CYP1A1	Cytochrome P450 1A1
• DDR	DNA damage response
• DNA-PK	DNA-dependent protein kinase
• DNAPKcs	DNA-dependent protein kinase catalytic subunit
• DSBs	DNA double-strand breaks

• ERCC2	Excision repair cross-complementing group 2 protein
• ERG	ETS related gene
• ET	Essential Thrombocythemia
• FISH	fluorescence in situ hybridization
• FLT3	fms-like tyrosine kinase 3
• GGR	Global Genomic Repair
• H2AX	Histone H2A variant
• HCC	Hepatocelular carcinoma
• HD	Hodgkin disease
• HR	Homologous Recombination
• HRR	Homologous Recombination Repair
• IPT	Immunophenotyping
• MAP	MYH-associated polyposis
• MDC1	Damage Checkpoint protein 1
• MDR	Multidrug resistance
• MLL	Mixed-lineage leukemia
• MMR	Mismatch repair
• MPNs	Myeloproliferative neoplasms
• MRN	NBS1-MRE11-RAD50 complex
• MSI	Microsatellite instability
• NBS	Nijmegen breakage syndrome
• NER	Nucleotide Excision Repair
• NHEJ	Non homologous end joining
• NPM	Nucleophosmin
• NSCLC	Non–small-cell lung cancer
• OS	Overall survival
• PAHs	Polycyclic aromatic hydrocarbons
• PARP	Poly ADP-ribose polymerase
• PCR	Polymerase Chain Reaction

• PR	Partial Remission
• PTD	Partial tandem duplication
• PV	Polycythemia Vera
• RD	Resistant disease
• RFS	Relapse free survival
• rhGCSF	recombinant human granulocyte colony-stimulating factor
• ROS	Reactive oxygen species
• RPA	Replication protein A
• SCT	Stem cell transplantation
• SNP	Single nucleotide polymorphism
• SSBs	Single strand breaks
• ssDNA	Single-stranded DNA
• SWOG	Southwest Oncology Group
• t-AML	Therapy related AML
• TCR	Transcription-coupled repair
• TFIIH	Factor II H
• t-MDS	Therapy related Myelodysplastic Syndrome Transcription
• TPMT	Thiopurine S-methyltransferase
• TTD	Trichothiodystrophy
• UV	Ultraviolet light
• XP	Xeroderma pigmentosum
• XPD	Xeroderma pigmentosum D
• XP/CS	Combined XP with Cockayne's syndrome
• XRCC1	X-ray repair cross complementing protein 1
• XRCC3	X-ray repair cross complimenting group 3
• XRCC4	X-ray repair cross complimenting group 4

List of tables

List of figures

Introduction:

Acute myeloid leukemia (AML) is a genetically heterogenous disease, in which somatic mutations that disturb cellular growth, proliferation and differentiation accumulate in hematopoietic progenitor cells, leading to increased number of immature myeloid cells in bone marrow (B.M.) ***(Mrozek et al., 2004).***

In recent years, DNA repair pathways that may protect against DNA damage from both endogenous and exogenous sources have been described. Whenever repair is ineffective, chromosomal instability may occur leading to either apoptosis or oncogenesis ***(Voso et al., 2004).***

The main four pathways for DNA repair according to ***Seedhouse et al. in 2004*** are mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), and DNA double strand break (DSB) repair.

It is now believed that an individual DNA repair capacity is genetically determined and is the result of combinations of multiple genes. Studies have noticed association between DNA repair genes polymorphism and risk of various types of cancers ***(Matullo et al., 2006)*** including AML and in particular therapy related AML (t-AML) ***(seedhouse et al., 2004).***

The most frequent type of gene polymorphisms is the so called single nucleotide polymorphism (SNP), in which one amino acid substitution occurs ***(Efferth et al., 2005).*** Several SNPs in DNA repair genes have been defined including XRCC1 Arg399Gln in BER pathway (***Seedhouse et al., 2004)***, also in NER pathway XPD Lys751Gln was described, while in DSB repair pathway RAD51 G135C and XRCC3 Thr241Met have been defined ***(Kuptsova et al., 2007).***

The XRCC1 Arg399Gln polymorphism was found to be a risk factor for the development of chronic obstructive pulmonary disease (COPD) ***(Yang et al., 2009)*** up to development of lung cancer ***(Li et al., 2008)***, also data from ***Kelsey et al. in 2004*** are consistent with a potential role of the *XRCC1 Arg399Gln* polymorphism in bladder cancer and high risk of Hodgkin disease (H.D.) ***(EL-Zein et al., 2009).***

Long el al. in 2009 found that individuals featuring the XPD genotypes with codon 751 Gln alleles were related to an elevated risk of hepatocelular carcinoma (HCC). Also it was found to be associated with esophageal adenocarcinoma ***(Tse et al., 2008)***.

The XPD codon 751 polymorphism is an independent prognostic marker for disease-free survival and overall survival in elderly AML patients treated with chemotherapy, and specifically that the glutamine variant was associated with a poorer prognosis relative to the lysine variant ***(Allan et al., 2004)***. Moreover XPD codon 751 glutamine encoding variant significantly

associates with risk of developing AML with a chromosome 5q or a chromosome 7q deletion ***(Smith et al., 2007).***

Seedhouse et al. in 2004 reported that a protective effect against AML in individuals who carry at least one copy of the variant XRCC1 399Gln allele compared to those homozygous for the common allele.

In a study made by ***Ozcan et al in 2008***, XPD-751Gln and also XRCC1-399 variants were detected that Gln/Gln genotype as a protector, and both decreased significantly in AML. In leukemias with early relapse, XPD 751 Lys/Lys genotype was observed to be at a statistically higher ratio (p=0.042).

Aim of work:

The aim of this work is to asses the frequencies and coincidence of XPD Lys751Gln and XRCC1 Arg399Gln polymorphism among newly diagnosed denovo AML patients and their association with response to induction therapy as well as with other prognostic factors.

Review of litrature