Chronic myeloid leukemia (cml) - a clonal myeloproliferative disease

Health & Medicine, Disease

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease resulting from neoplastic transformation of multipotent stem cell. The disease is characterized by high levels of leukocytes, splenomegaly, myeloid hyperplasia in bone marrow and high levels of mature myeloid cells in peripheral blood (Elhoseiny et al., 2014). In 95% of CML cases, chromosomal translocation resulting in the formation of the Philadelphia (Ph) chromosome is observed (Lakkireddy et al., 2015).

This chromosome is created by a reciprocal translocation t(9; 22)(q34; q11), which transfers the Abelson (ABL) oncogene on chromosome 9 to the breakpoint cluster region (BCR) of chromosome 22, resulting in the formation of a fused BCR/ABL gene (Al-Achkar et al., 2014). The protein encoded by the fusion gene exhibits enhanced tyrosine kinase activity and plays a key role in the initiation and maintenance of CML by activating various intracellular signaling pathways resulting in uncontrolled proliferation, decreased apoptosis and survival of leukemic stem cells (Lakkireddy et al., 2015)CML affects males more than females and usually occurs in middle-aged adults. It is known that the environmental exposures to cytotoxic and genotoxic agents, particularly those derived from benzene and ionizing radiation, may be associated with increased risk of CML (Taspinar et al., 2008).

Xenobiotics are chemical substances that are foreign to the biological system. They include naturally occurring compounds, drugs, environmental agents and carcinogens. In order to avoid accumulation of lipophilic xenobiotics in cells and tissues, enzymatic reactions of xenobiotic metabolism are needed (Taspinar et al., 2008). Xenobiotic metabolizing

enzymes (XMEs) constitute one of the first lines of defense against environmental chemicals. They play a central role in the metabolism, elimination, and detoxification of xenobiotics or exogenous compounds introduced into the body (Omiecinski et al., 2011).

Cells have developed an effective mechanism to prevent accumulation of damaging xenobiotics by way of their elimination catalyzed by multiple enzyme system. The enzymes of the multiple enzyme system are classified in two categories namely Phase I and Phase II (Elhoseiny et al., 2014). The key enzyme systems catalyzing phase I oxidative metabolism are enzymes of the cytochrome P450 (CYP) superfamily. During these reactions, toxic metabolites are generated which might be processed by phase II enzymes (Taspinar et al., 2008). Phase II is catalyzed often by the ‘‘ transferase’’ enzymes that perform conjugating reactions. The products of phase II conjugations are typically more hydrophilic than the parent compounds and therefore usually more readily excretable (Omiecinski et al., 2011).

Glutathione S-transferases (GSTs) are major phase II detoxifying enzymes and are able to perform a wide variety of functions (Davies, 2002). GSTs fall into two distinct superfamilies: membrane bound microsomal GSTs and the soluble or cytosolic GSTs. The cytosolic glutathione S-transferase were classified into eight classes on the basis of sequence diversity and designated as Alpha (α), Mu (μ), Pi (л), Kappa (K), Theta (θ), Omega (O), Sigma (ε) and Zeta (Z). These cytosolic enzymes play major role in detoxification of activated carcinogens (Sailaja et al., 2010). Glutathione S-transferase P1 (GSTP1) belongs to the pi class gene family, located on

chromosome 11 (11q13)(Autrup, 2000). It comprises of 7 exons that encode for cytosolic GST enzyme (Dunna et al., 2014). GSTP1 is considered as major antioxidant present in both the epidermis and the dermis, overexpressed in a variety of preneoplastic and neoplastic tissues (Sailaja et al., 2010). GSTP1 gene possesses two variations in coding region, an A→G transition at105 codon and a C→T transition at 114 codon. (Sailaja et al., 2010).

The A→G polymorphism at nucleotide 313 in exon 5 of GSTP1 lead to an amino acid substitution of isoleucine (Ile) by valine (Val) at amino acid position 105 (Ile105Val). This substitution potentially diminished the ability to detoxify certain mutagens and mutations and hence a greater risk of developing cancer (Dunna et al., 2014). Biochemical studies have indicated that the conjugating activity is lower for Val homozygotes than of Ile homozygotes, with heterozygotes displaying intermediate activity. Individuals with at least on Val allele might have an underlying predisposition toward cancer when the exposed to environmentally derived or endogenously formed GSTP1 substrates (He et al., 2014). This study aimed to determine the genetic polymorphism of GST P1gene and its association with chronic myeloid leukemia among Sudanese population.