Survey on the Oxidative Stress Status and the Role of Antioxidants in Acute Myeloid Leukemia Therapy

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Abstract

Acute myeloid leukemia (AML) is a heterogeneous disease with multiple mutations in hematopoietic stem cells characterized by abnormality increases in immature or dysfunctional white blood cells. The precise mechanisms of AML development have not been clear but there are many factors increase to developing leukemia such as familial history of leukemia, elderly, life style, genetics and some chronic disease like diabetic. Multiple mutilations happen in the hematopoietic stem cells, acquire some form of genetic instability lead to improve expression of some protein kinase and transduction protein following that increase ROS formation, which is associated with increased DNA damage. Nowadays, the use antioxidant drugs are growingly accepted in universal due to their safety and efficiency to diminish the adverse effects of free radicals and treatment of the many diseases such as cancer. In this article, we discussed the correlation between acute myeloid leukemia incidence and the oxidant biomarkers (oxidative stress), and more focusing on the great role of antioxidant biomarkers, whether the non-enzymatic or the enzymatic in the protection of the cells against harmful effects of free radicals in the acute myeloid leukemia patients.
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Keywords: Acute Myeloid Leukemia; Oxidative Stress; Antioxidant

Introduction

Leukemia is characterized as a hematological clonal malignancy triggered by excessive irregular leukocytes in the tissue of the bone marrow. Acute myeloid leukemia (AML) is a multi-molecular heterogeneous disorder and is distinguished by uncontrolled proliferation without differentiation from the myeloid progenitor cell (1).The development of malignant cells inside the bone marrow, peripheral blood and occasionally in other organs applies to clinical manifestations for AML. Most patients have a combination of leukocytosis symptoms and bone marrow dysfunction, such as anemia and thrombocytopenia. Common complaints include fatigue, anorexia and weight loss; lymphadenopathy and organomegaly are not normally seen (2).

AML is the world's most lethal form of leukemia, with 147,000 mortality recorded in 2015 by Global Burden of Disease collaborations. AML is correlated with almost 30% of leukemia incidents and around 40% of leukemia-associated deaths. The probability AML has risen in the past decade (3). It was worth noting also, that the treatments of AML include different strategies, which involved the intensive chemotherapy, radiotherapy, stem cell transplantation, and immunotherapy (4).Importantly, under the chemotherapy treatments, the most adult AML patients have achieved complete remission; while only few of patients have achieved long-term disease-free survival, for most of the deceased patients have died of refractory or recurrent AML (5).Therefore, it is necessary to develop new treatments that can prolong the disease-free survival of AML patients, which may have an ability to improve the immune system such as antioxidant drugs (vitamin and minerals) in parallel with the routine treatment. For this reason, the aim of this study was to describe the clinical characteristics, diagnostic criteria,

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pathophysiology, treatment strategies, the influence of oxidative stress and antioxidants in acute myeloid cancer.

1-Etiology

A variety of risk factors for AML include increased age, gender, diet, genetic abnormalities, chronic illness, smoking, diabetes mellitus and obesity (3,6,7,8,9).

1-1-Gender

In both males and females, the prevalence rate of cancer substantially increases with age. According to Surveillance, Epidemiology, and End Results (SEER) statistics males are 1.6 times more likely than females to be diagnosed with AML, with an age-adjusted prevalence of 5.42 and 3.47 per 100,000 males and females, respectively (6). The higher cancer risk observed was originally attributed to increased male exposure to various carcinogens such as smoking, alcohol consumption and sun exposure (7).

1-2-Age

AML occur commonly an elderly age. For people aged 65 years or above, the age-adjusted rate is 20.1 per 100,000 person-years compared to 2.0 per 100,000 person-years for those younger than 65 years. A median age at diagnosis of 62 years was found through a study of SEER data of AML patients from 2001 to 2013 with an established WHO classification, while a more recent review focused on 2011-2016 data indicates a median age of 68 years for AML diagnosis(6).The elderly population is more susceptible to oxidative disruption due to the decline of antioxidant molecules and also certain foods, such as antioxidant vitamins and polyphenolic compounds, are more difficult reabsorption for older people (8).

1-3-Residence area

It is suspected that the variable elevated risk of AML is correlated with a wide variety of environmental and chemical exposures. For example, radiation exposure is correlated with AML, for example. In survivors of atomic bomb blasts in Japan, an increased frequency of AML was observed, with a peak of 5 to 7 years after exposure (9).

1-4- Way of living

The way of living, in addition to exposure to chemicals, can affect the risk of AML and ALL development. While the pathophysiological mechanisms are uncertain, smoking and becoming overweight have been found to increase the risk of acute leukemia (10). The fundamental biochemical function remains unknown. This may be attributed to the promotion of tumorogenesis by insulin resistance and improved pancreatic insulin secretion also, impaired immune function due chronic inflammation can be involved this process (11).

1-5-Genetic conditions

Several hereditary disorders have been linked with acute leukemia. AML has previously been reported to be correlated with chromosomal rearranging, but new analyses of tumor genotypes have shown that genetic variations can play a significant role in tumorigenesis (3). There are a series of syndromes which consequently of genetic abnormalities present at birth, can enhance the possibility of leukemia. These involve black fan-diamond disease, anemia of Fanconi, Bloom Syndrome and Down syndrome or chromosome 21 abnormality (12).

1-6-Diabetic disease

Some epidemiological studies have investigated the risk of leukemia among diabetic patients, but the results were unpredictable. Systematic reviews in 2012 revealed a 22 per cent increase in risk of leukemia in patients with type 2 diabetes mellitus (T2DM) particularly in comparison to the euglycemic population. The incidence of leukemia was significantly increased in patients suffering from T2DM for 1–5 years and 5.1–10 year (13).

2-Pathophysiology

All blood cells derive from blood stem cells with the myeloid pathway in the natural phase, generating red blood cells, platelets and white blood cells and the lymphoid pathway producing multiple forms of lymphocytes. Disturbance of this equilibrium due to different conditions and environmental factors can lead to irregular cell division and generation of abnormal cells and the appearance in circulation of heterogeneous populations of genetically distinct sub-clones associated with particular types of tumors (14). Chromosome translocations are observed in the genome such as t (8; 21), t (15;17), t(16;16) or inv16 are common Chromosomal mutations are identifying in various kinds of tumors like AML. Additional mutational studies have shown that obligatory mutations (Fms-like tyrosine kinase with internal tandem duplications (FLT3-ITD) and CCAAT/enhancer alpha protein is happening (14) (15). FLT3 is involved in driving increased ROS development (16). In hematopoietic stem cells, ROS-related metabolic processes, such as polyamine metabolism, cytochrome P450 and xanthine oxidase, produce ROS in the mitochondria (17). However, over production of free radicals have toxic effects on stem cell, resulting in dysfunctions like irregular proliferation and

differentiation and mediates damage to the composition of cells and membranes, DNA, lipids, and proteins (17) (18).

3- Oxidative Stress and Antioxidants

Human health is affected by free radicals and reactive oxygen species (ROS), which are critically involved in the incidence of various pathological conditions such as cancer, hypertension, cardiovascular disorders, arthritis, inflammation, liver diseases and other illnesses (19,20).

The oxidative stress (OS) resulted from these reactive oxygen species has been defined by an imbalance between generation of ROS and the capacity of the biological system to repair or neutralize oxidative damage including peroxide (H2O2) and free radicals (O2-). In patients with cancer, oxidative stress plays a critical and important role, especially in the stages of diagnosis and medical treatment (14). Indeed, the OS status has been linked to the development and pathogenesis of many human metabolic and chronic disorders in addition to the cancer (21). In this respect, it was worth mentioning also, that there are two main lines of defense against ROS: 1- Formation of antioxidant enzyme, such systems include superoxide dismutase, catalase and glutathione peroxidase. The activity of these enzymes, in turn depends on the supply of manganese, copper, zinc or selenium, 2- Defense system that depend directly on antioxidant nutrients containing vitamin E, vitamin C, carotenoids and flavonoids (22). Nowadays, the use of herbal drug and their derivatives with high levels of antioxidant components are growingly accepted in worldwide due to their safety and efficiency to minimize the adverse effects of free radicals and treat diseases (23).

Malondialdehyde

Malondialdehyde (MDA) is a bisdimethylacetal, which consists of three low molecular weight aldehyde carbons and a spontaneous peroxide breakdown product that can be produced by a free radical attack on polyunsaturated fatty acids. MDA is the main product of peroxidation of membrane lipids; it can also act as accurate biomarker of oxidative stress. Al-Ubadi et al., showed elevation of the malondialdehyde concentration to some Oxidant and antioxidant in leukemia patients (24). This indicated rising in lipid peroxidation in leukaemia patients is attributable to oxidative stress due to free radical production (25). The amounts of plasma MDA serve as an essential leukemia biomarker with a diagnostic, prognostic and disease progression (26). In patients with AML, high O2– levels in the leucocytes may be linked with increased MDA levels at the same time (15). In patients with post-treatment neoplasm, malondialdehyde elevation among the types of cancers studied may reflect the stimulation of the immune system induced by toxic compounds used in chemotherapy or radiation with a high frequency of radiotherapy treatment that triggered overproduction of free radicals (24).

Xanthine oxidase

Xanthine oxidase, which catalyzes the oxidation of hypoxanthine to xanthine and further xanthine to uric acid in the ROS generation. Xanthine oxidase is a main peroxisome system enzyme that has been shown to generate ROS as well as RNS (16). In spite of the structural variations and substrate specificity, ROS as a secondary product may be generated by both types of the enzyme. XDH would contribute primarily to the production of superoxide (O2-), while XO would ultimately produce hydrogen peroxide (H2O2). Different forms of solid tumors have been connected to down regulation and upregulation of XOR function, indicating the role of ROS generated by XOR in tumorigenesis. In addition, chronic myeloid leukemia has been associated to higher XO activity (27).

Superoxide Dismutase

Superoxide dismutase (SODs) are most powerful antioxidant in the body and plays a major role in regulating the cell's redox state. It is an essential endogenous antioxidant enzyme that performs against ROS as part of the first-protection process. SOD is a metalloenzyme and therefore requires a metal cofactor for its activity. SODs primarily present in the cytoplasm, but even in peroxisome. SOD protects immune system and significantly reduces the risk of infection and slows down aging rate and have been recommended proper daily SOD supplement (28). One of the earliest studies that indirectly linked ROS to the pathogenesis of AML revealed that the levels of SOD in AML cells were decreased comparison to normal granulocytes (16). Huang et al., also reported that SOD inhibition activated of the O2 aggregation and contributed readily to free radical-induced apoptosis in human leukemia cells. Mn-SOD involvement in AML cells in this study is poor in comparison with regular granulocytes and monocytes. The findings indicate that the reduction in the function of Mn-SOD in cells of AML can predispose mitochondrial membranes to oxidative stress (29). Nishiura et al., reported elevated serum SOD activity in acute leukemia and indicated that regression of the leukemia was accompanied by a decrease in the serum level of SOD. These findings suggest that enzymatic antioxidant defenses are impaired and interfere with the direct elimination of free radicals and the defense of biological sites (14).

Glutathione

The most significant antioxidant synthesized by cells is glutathione (GSH). Glutathione is present either as reduced (GSH) or oxidized (GSSG) type, and is an important factor in controlling the redox. Under physiological conditions, the predominant form of reduced GSH is 10- to 100-fold higher than the oxidized types. The GSH: GSSG ratio is usually maintained above 100:1, but during oxidative stress conditions, reach less than 4:1 (30). The conversion of GSH to GSSG is catalyzed by Glutathione peroxidase. In the cases of low cell GSH, GSSG is reduced to GSH by reaction using NADPH and a redox cycle is developed. GSH or GSH/GSSH loss or decreased value contributes to OS involving the progression of cancer. In comparison, high GSH improves the antioxidant potential which results in OS resistance in cancer cells. In hematological malignancies, GSH elevation has been found in chemo resistance to daunorubicin, melphalan and prednisolone (17). The decreased amounts of GSH in the case of leukemia represent the degradation of the non-enzymatic antioxidant reserve. It indicates that the depletion of GSH usually functions as an antioxidant mechanism, whereas reduced plasma amounts of GSH could be attributed to hematopoietic cell overproduction of ROS (26). A GSH reduction or decreased GSH/GSSH ratio contributes to OS, which is involved in the progression of cancer (31).

Glutathione peroxidase-1

Glutathione peroxidase-1 (GPX1) is a selenium-dependent enzyme, H2O2 scavenger which is distributed between the mitochondria and cytosol that helps to preserve redox equilibrium within cells. It mainly protects organisms from oxidative damage through the reduction of lipid hydroperoxide and free hydrogen peroxide. In mammalian, currently eighth GPX sub-members have currently been recognized. They play a major role in restoring damage induced by reactive oxygen species (ROS) and DNA, protein and lipids protect from oxidative and carcinogenesis (32). Mantovani et al., found a rise in oxidative stress during leukemia incident by leukemia as compared with controls. The analysis proves that glutathione peroxidase GSH-Px, vitamin E and selenium, which are antioxidant compounds, represent an essential function in the elimination of reactive oxygen species, hydrogen peroxide, hydro fatty peroxide and free radicals. However, high intracellular ROS levels may contribute to increased DNA mutations associated with increased carcinogenesis (33).

Catalase

The other major regulator of intracellular ROS is catalase (CAT) enzymes. They change hydrogen peroxide into oxygen and water and are located mainly in cytosols and peroxisomes (16). Overexpression of CAT is cytoprotective to cells, as it increases life expectancy and decreases ROS-induced injury. However, in leukemia, alteration of CAT may lead to increased proliferation, genomic instability, and drug resistance. The increase or decrease in catalase activity has different implications on both myeloid and lymphocytic type of the leukemia. In AML cell lines and CML specimens, there was an elevation in CAT level relative to normal granulocytes. When CAT activity rises, ROS levels fall. Contrarily, when CAT activity falls, ROS levels are rising and associated with impaired DNA and genomic instability (17).

Paraoxonase

Serum paraoxonase-1 (PON1) is 45 kDa of glycoprotein have Calcium-dependent esterase activity catalyze organophosphate hydrolysis and commonly found in tissues like the kidney, liver, intestine, and serum, where it has been related with HDL. PON1, the lipophilic antioxidant portion of HDL cholesterol, has been shown to reduce LDL's sensitivity to lipid peroxidation through its antioxidant action, which prevents lipoproteins from oxidation. ÇEBI et al., assessed paraoxonase levels in patients with AML against healthy control outcomes. The results are shown that the serum PON1 activity was not altered in all categories (34).

Metallothionein

The metallothioneins (MTs) are a group of intracellular cysteine rich, low-molecular weight proteins that sustain intracellular metal homeostasis by binding metals, including zinc and copper, detoxification, redox equilibrium and as well as act anti-oxidants protect against DNA destruction and apoptosis. Low expression of MT in liver, colon and prostate cancer has been reported. Recently, it has been shown that Overexpression of MT-type 1 has significantly restricted promyelocytic leukemia-induced by retinoic acid (35). Different isoforms of MT have been identified, classified into four groups (MT1-4) based on small differences in sequences and characteristics of the protein. MT3 was first described as an inhibitory element in neuronal development. In vitro studies have shown that MT3 can constrain neuritis formation and neuronal survival. The new study established the epigenetic inactivation of MT3 through hypermethylation of the MT3 promoter in both AML cell lines and pediatric AML samples. Results indicated that overexpression of MT3 transcriptional could inhibit proliferation in AML cells and induce apoptosis (36). Hence, MT isoforms profiling status could be utilized for diagnostics and therapy of tumor diseases (37).

Ceruloplasmin

Ceruloplasmin oxidase is an alpha2 glycoprotein, part of the class of multi copper oxidase. Ceruloplasmin is synthesized in the liver possessing 6 copper atoms in its structure which carries more than 95 percent of the overall in human plasma of copper. The remaining is compensated by macroglobulin. It has multiple functionalities in the human body such as ferroxidase action, elimination of plasma free iron, defense of blood and lipid membranes from oxidative damage as antioxidant and in patients with chronic diseases, leukemia and other malignant tumors, increasing levels are detected. In study research on rats, Davis and Johnsonn demonstrated that low copper dietary consumption contributes to a decline in serum ceruloplasmin levels, enhancing the sensitivity of these animals to colon cancer (38).

Gadjeva et al., reported substantial elevations in ceruloplasmin activity levels in patients with malignant hematological diseases in comparison to healthy control. Abdul-Barry J. and his team evaluated ceruloplasmin activity and two trace elements in the of various forms of malignancies, they found that levels of this enzyme were arise at cancerous patients and recommended the enzyme's activity as a useful predictor for evaluating the seriousness of malignancy. Al-Kazzaz has studied that levels of ceruloplasmin enzyme activity had been found increased in patients with leukemia form of all, AML and CML (24).

Vitamin E

Vitamin E (alpha-tocopherol) is a low molecule substance with antioxidant action against free radicals and oxidants. It is found in saturated and unsaturated fats in foods from both plant and animal sources. This material, which is absorbed by blood via the lymphatic system, reaches the liver where it is preserved. Vitamin E inhibits cellular and tissue degradation through eliminating free radicals, protects cellular membranes from oxidation and prevents micro clot production and blocks nitrosamine creation. Epidemiological studies indicate that the concentration of tocopherol in the blood or in food is associated with mortality from neoplastic disorder (6).In patients with leukemia, vitamin E deficiency is associated with elevated ROS concentration in the biological system causative Oxidative stress. Deepti et al., indicated that vitamin E and A, together with SOD, CAT, GPx, are dramatically decreased in leukemia. These results also indicate that antioxidant enzymes, along with vitamin E and A, support the biological process against ROS. In leukemia, vitamin E levels are lower than normal control individuals, not only for ALL and AML, but also for CLL and CML. One of the main factors, malnourished individuals have reduced immune and hematopoietic systems causes to vitamin E deficiency (26). Another study showed that glutathione peroxidase GSH-Px concentration, selenium and vitamin E concentration demonstrated a substantial decrease significantly in both male and female leukemia patient's comparison with the control group. However, high levels of intracellular ROS may result in increased DNA mutations related to increased tumorigenesis (33).

Vitamin C

Vitamin C (VC) or ascorbic acid is essential vitamin that possesses effective benefits, such as anti-aging, antioxidant and anti-cancer. Li et al., found VC protects against PFOS-associated leukemia by preventing the proliferation of leukemia-associated cells and tumor formation (39). Vitamin C causes oxidation GSH to its oxidized type GSSG. As a consequence, concentration-dependent H2O2 developed in parallel with the activation of apoptosis. The direct role of H2O2 in inducing apoptosis in AML cells was shown (40).

Trace Elements

Iron (Fe), zinc (Zn), copper and selenium are essential cofactors for the reliability of DNA in a variety of enzymes. Furthermore, they are involved in membrane transport, nerve conduction and muscle contraction and also in the function of sub-cellular systems such as mitochondria, and also act as antioxidants. The abnormal amounts of these trace elements might interfere with biological progression (2).

Copper

Copper is an important trace element in the living organism and its main responsibility is it is one of the catalytic cofactor in biological processes. Copper is an essential part of many metalloproteins as cytochrome C, ceruloplasmin, cytochrome oxidase and superoxide dismutase. In several tumor forms, including cervical, breast, ovarian, prostate, stomach, cancer and leukemia elevated amounts of copper in cancer have been identified (41). One study is demonstrated copper concentrations were significantly higher in the cancer patients with AM Land ALL than in healthy group although serum levels of selenium and zinc were decreased. Copper level is elevated in cancers, lymphomas, sarcomas, leukemia and Hodgkin's disease (42). Copper can catalyze the formation of highly reactive hydroxyl radicals from H2O2 during Haber-Weiss reaction, which leads to lipid oxidation and the production of peroxyl and alkoxyl

radicals (25). There is evidence that serum copper could be useful for assessing the degree of cancer, which might be indicative of chemotherapy reaction (42). In 2015, Dayer findings indicated higher serum copper levels than patients with control individual, this research have been agreed with the results of Paulo et al., (2006) and Qunzhi et al., (2001), who suggested that patients with acute myeloid leukemia, acute lymphoblastic leukemia, and lymphoma had higher serum copper level (43).

Zinc

Zinc is an essential component of immune resistance preservation and required for various biochemical enzymes, such as metalloenzymes, and for proper immune system function (25) In malignant diseases, laboratory findings support a reduction in zinc concentrations. Demir et al., found reductions in Zn levels in patients with acute leukemia comparison to control subjects (42). In review, Tahir and abed 2019 detected reduction in the concentration of Cu and Zn in AML patients relative to control in according with previous results(2).In certain study, plasma levels of, Fe, Se, Zn, MDA and SOD were significantly higher in patients with acute leukemia comparative to controls, while slightly lower plasma levels of Cu were found in patients with leukemia (25).

Selenium

Selenium (Se) is an essential sulfur homologous trace element with a high chemical activity. Selenium is a necessary component of two critical enzymes: glutathione peroxidase and thioredoxin reductase. Animal experiments study have shown that treatment with selenium decreases tumor recurrence, prevents cell growth and angiogenesis. Se deficiency leads to a higher incidence of cancer because it down-regulates proto oncogenes and up-regulates tumor suppressor genes and apoptosis. Se serve as a GPX cofactor, and has a considerable function to preserve appropriately low amounts of H2O2, so, prevent free radical accumulation in the body cells (41,44). Asfour et al., found that levels of Se and GPX activity decreased in patients with AML that agree with Zuo et al., Lower dietary intake and increased requirements due to stress from the cancer might explain the decreased serum Se and GPX activity. Moreover, the tumor cells may take up more selenium (44).

Manganese

Manganese is very essential for cellular processes and many enzymes require it as cofactor Mn-superoxide dismutase (Mn SOD) is an endogenous antioxidant enzyme that neutralizes free radicals and avoids cellular damage. Antioxidant defenses are reflective of enhanced free radical generation in leukemic patients and decreasing antioxidant defenses. Elevated of Mg after cytotoxic therapy of malignant cells indicate the correlation between the deficiency of this element and the production of neoplastic disorders (2). Moreover, in vitro and in vivo studies indicated that the antioxidant minerals such as manganese(II) chloride (MnCl2) treatment- promote mitochondrial lipid peroxidation in tumor cells and ROS production by releasing type-I IFNs that reduce dihydroorotate dehydrogenase function and thereby inducing ferroptosis in tumor cells. Which may provide a novel strategy to complement existing antitumor treatment regimens (45). This mechanism has gained attention in the field of antitumor research after Dixon et al., (2012), demonstrated that erastin-induced cell death in RAS-mutant tumor cell lines occurs through ferroptosis (46).

Conclusion

Acute myeloid leukemia (AML) is a malignant neoplasm of hematopoietic cells characterized by an abnormal proliferation of myeloid precursor cells, an arrest in cellular differentiation. In leukemia is also caused by OS, and is associated with genetic abnormalities, chromosomal changes and increases ROS, leading in tumorigenesis. Identifying biological changes in cancer cells caused by anticancer drugs is meaningful to improve their therapeutic effect. Additionally, anticancer drugs cannot distinguish between cancer cells and healthy cells, which are thought to be a reason for chemotherapy's negative side effects. For this reason, patients receiving cancer treatment often seek complementary and alternative adjuvant therapies to reduce side effects and improve quality of life. A popular group of complementary therapies used by patients with cancer is antioxidants, which can be administered through dietary interventions, intravenous infusion or most commonly, dietary supplementation. Antioxidants are substances that act to prevent or delay cellular damage, notably by stabilizing free radicals and reducing oxidative stress. Antioxidants are a successful approach to overcome the production of hematological malignancies. Unregulated or down regulated of antioxidant is established in leukemia patients. Up regulation of antioxidants function enhance leukemia's resistance to harmful ROS consequences and down regulation of antioxidants activity facilitate progress of cancer cells survival and increases heterogeneity have been recorded. Hence, the usage of antioxidant drugs in the treatment of leukemia is being explored and has been preliminarily applied and could be utilized as promising diagnostics and therapy of tumor diseases.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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