

Oxidative stress response induced by chemotherapy in leukemia treatment (Review)

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Abstract. Oxidative stress (OS) has been linked to the etiology and development of leukemia as reactive oxygen species (ROS) and free radicals have been implicated in leukemogenesis. OS has beneficial and deleterious effects in the pathogenesis and progression of leukemia. High-dose chemotherapy, which is frequently used in leukemia treatment, is often accompanied by ROS-induced cytotoxicity. Thus, the utilization of chemotherapy in combination with antioxidants may attenuate leukemia progression, particularly for cases of refractory or relapsed neoplasms. The present review focuses on exploring the roles of OS in leukemogenesis and characterizing the associations between ROS and chemotherapy. Certain examples of treatment regimens wherein antioxidants are combined with chemotherapy are presented, in order to highlight the importance of antioxidant application in leukemia treatment, as well as the conflicting opinions regarding this method of therapy. Understanding the underlying mechanisms of OS generation will facilitate the elucidation of novel approaches to leukemia treatment.

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1. Introduction

Oxidative stress (OS) refers to the cellular environment conditions that result from an imbalance between the generation of reactive oxygen species (ROS) and the response of the antioxidant defense systems (1). ROS are short-lived highly reactive molecules and serve a critical role in the progression of OS. ROS were identified as free radicals for the first time in 1954 by Gerschman (2). They are metabolites produced during normal cellular processes, which serve important roles in activities such as promoting health and longevity (3) and antimicrobial phagocytosis by cells of the innate immune system (4,5). The over-generation of ROS without an adequate response from the innate antioxidant system to maintain the homeostasis eventually leads to OS. ROS serve a dual role in tumorigenicity, particularly in hematologic malignancies. ROS can induce the activation of cell death processes, including apoptosis, which provides a mechanism for cancer treatment (6); however, it can also facilitate carcinogenesis by protecting the cell from apoptosis and promoting cell survival, inducing proliferation (7), migration (8), metastasis (9) and drug-resistance (10,11). It has been reported that OS is involved in the development of a number of hematologic malignancies, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia (ALL) (12-16). Numerous methods including the use of chemotherapeutic agents and radiation are reported to generate ROS or other free radicals in patients undergoing cancer therapy.

The present review focused on exploring the role of OS in leukemogenesis and determining the association between ROS

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and chemotherapy, as well as highlighting the importance of antioxidant application in leukemia treatment. Improving current understanding of the underlying mechanisms of OS generation in leukemogenesis will facilitate significant progress in developing novel therapeutic measures for various types of leukemia.

2. OS and the generation of ROS

OS is a biochemical condition that occurs when intracellular antioxidants are unable to neutralize pro-oxidants, such as ROS. Mitochondria are the primary sites for oxidative phosphorylation, which produces massive highly reactive and unstable oxygen, thus oxidizing a large number of molecules to form ROS (17). ROS are generated intracellularly within various compartments and through multiple mechanisms (Table I). Mitochondria-derived ROS consist of singlet oxygen (O_2), superoxide anions ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), nitric oxide (NO^{\bullet}), hydroxyl radicals (OH^{\bullet}) and hydroxyl ions (OH^-). The generation of mitochondria-derived ROS is presented as a schematic in Fig. 1. Initially, oxygen is catalyzed to transform into a superoxide anion by xanthine oxidase (XO) (17,18), or by mitochondrial respiratory chain complexes I (NADH dehydrogenase) and III (bc1 complex) either in the matrix or in the intermembrane space (19). Subsequently, the superoxide anion is converted to H_2O_2 by superoxide dismutase (SOD). H_2O_2 can be detoxified to H_2O and O_2 with glutathione peroxidase, catalase (CAT) or thioredoxin peroxidase (TPx) (20). It can also be transformed into an OH^{\bullet} and an OH^- via the Fenton reaction (21).

3. Basic ways OS causes cell injury

OS causes cell injury predominantly via the following three basic pathways: Lipid peroxidation of membranes; oxidative modification of proteins; and DNA damage (17). Lipid peroxidation affects cell membranes and other lipid-containing structure via a process known as the 'chain reaction of lipid peroxidation'. The critical intermediate products of this reaction are hydroperoxides (LOOHs), which can disturb the membrane structure and endanger cells (22,23). It has been reported that the direct secondary products of lipid peroxidation are aldehydes, malondialdehyde (MDA) and 4-hydroxynonenal/4-hydroxy-2-nonenal (HNE) (24). These products are considered to be the markers of OS, and their unique property of a no-charge structure allows them to easily permeate through membranes and into the cytosol, thus causing far-reaching and damaging effects inside and outside the cells, rendering them superior to ROS (25,26). There is evidence that HNE and MDA can cause protein or nucleic acid damage by modifying the amino acid residues to form stable adducts or covalent adducts with nucleic acids and membrane lipids (27,28).

Oxidative modification of proteins is another pathway by which OS causes cell damage, and thus serves a critical role in aging and cancer (29). MDA and HNE can react with and covalently modify numerous proteins, including amyloid- β peptide, collapsing response mediator protein-2 (CRMP2) and heat shock protein 70 (HSP70) (17,27,28). HNE- and MDA-protein adducts, including alpha-enolase (ENO1),

phosphoglycerate kinase 1 (PGK1), triosephosphate isomerase (TPI) and pyruvate kinase (PK), are reported to be involved in cellular senescence and cancer (30-33). Besides MDA and HNE, ROS-mediated protein oxidation also can be measured via the concentration of carbonyl groups, advanced oxidation protein products (AOPPs), advanced glycation end products (AGE) and S-nitrosylated proteins, which are considered to be novel markers for OS due to their long half-life and their ease of detection (34).

With respect to oxidative DNA damage, ROS and products of lipid peroxidation can have an effect on genomic and mitochondrial DNA, leading to various types of DNA damage (35,36). The replication of damaged DNA prior to repair results in DNA mutations and genomic instability, subsequently leading to a variety of disorders and tumorigenesis. The molecule 8-oxoGuanine (8-OHG) and its nucleoside form 8-OHdG are considered to be indicators of oxidative DNA damage *in vivo* and *in vitro* (37,38). The presence of 8-OHG in the DNA caused a G-T and a C-A transversion, as 8-OHG allows the incorporation of cytosine and adenine nucleotides opposite the lesion during DNA replication (39,40). Numerous studies have reported that 8-OHG/8-OHdG is involved in carcinogenesis and altered level of them demonstrated an association with pathogenesis of aging associated disease and cancer (41-43). For example, Ames and colleagues have found the age-dependent accumulation of 8-OHdG in DNA from various aged rat organs (44) and increased levels of 8-OHdG and OH8Gua were shown in senescent human diploid fibroblast (45). Mitochondrial dysfunction and the lack of protective mechanisms mean that mitochondrial DNA can be more easily and extensively exposed to ROS than nuclear DNA, which can result in irreversible DNA damage. In general, ROS and other OS-products attack cells through a variety of intricate pathways. The lipid peroxidation of membranes, the oxidative modification of proteins and DNA damage are the major known mechanisms for oxidative cell damage. Improved understanding the molecular mechanisms associated with OS will assist in the development of novel and reliable treatments, as well as preventive measures, for various types of cancer, particularly for leukemia.

4. Dual role of OS in leukemogenesis

Leukemia develops when hematopoietic stem cells (HSC) lose the capacity to differentiate normally into mature blood cells at various stages during maturation and differentiation (46). Hypoxia has emerged as a key regulator of stem cell biology and maintains HSC quiescence with a condition of metabolic dormancy based on anaerobic glycolysis, which causes low production of ROS and high antioxidant defense (47,48). While hematopoietic cell differentiation is accompanied by changes in oxidative metabolism, including a decrease in anaerobic glycolysis and an increase in oxidative phosphorylation, thus producing high levels of ROS (49-51). Furthermore, evidences have indicated that leukemia stem cells (LSC) are more dependent on oxidative respiration and are more sensitive to OS, compared with normal HSCs (16). Although OS has been linked to the etiology and development of leukemia, numerous chemotherapeutic drugs exert their biological effects via the induction of OS in affected cells. Thus OS

Reactive oxygen species

Reactive oxygen species	Intracellular sources	Compartment
O_2	<p>Fenton reaction</p> <p>Lipid peroxidation chain reactions</p> <p>Haber-Weiss reaction</p> <p>Superoxide dismutase (SOD)-mediated reaction</p> <p>Catalase-mediated reaction</p> <p>Glutathione peroxidase-mediated reaction</p> <p>Xanthine oxidase (XO)-mediated reaction</p>	<p>Mitochondria</p> <p>Cytosol</p> <p>Peroxisomes</p> <p>Nucleus</p> <p>Plasma membrane</p> <p>Endoplasmic reticulum</p> <p>Lysosome</p> <p>All membranes</p>
$OH\bullet$	<p>Proton-catalyzed decomposition of peroxynitrite</p> <p>Fenton reaction</p> <p>Haber-Weiss reaction</p> <p>Decomposition of ozone (O_3)</p> <p>Beckman-Radi-Freeman pathway</p> <p>Superoxide dismutase (SOD)-mediated reaction</p> <p>NADPH oxidase-mediated reaction</p>	<p>Mitochondria</p> <p>Cytosol</p> <p>Endoplasmic reticulum</p> <p>Lysosome</p>
H_2O_2	<p>Cytochrome P450-mediated reaction</p> <p>Xanthine oxidase (XO)-mediated reaction</p> <p>Monoamine oxidases (MAO)-mediated reaction</p> <p>Peroxisomal fatty acid oxidation</p> <p>Flavin adenine dinucleotide (FAD)-mediated reaction</p> <p>Antibody-catalyzed water (H_2O) oxidation</p> <p>Electron-transfer flavoprotein pathway</p>	<p>Mitochondria</p> <p>Cytosol</p> <p>Peroxisomes</p> <p>Plasma membrane</p> <p>Endosomes</p> <p>Endoplasmic reticulum</p> <p>Lysosome</p> <p>Nucleus</p>
$O_2^{\bullet-}$	<p>Fenton reaction</p> <p>NADH/NADPH oxidase (NOX)-mediated reaction</p> <p>Xanthine oxidase (XO)-mediated reaction</p> <p>Lipoxygenase pathway</p> <p>Cyclooxygenase pathway</p> <p>Cytochrome P450 monooxygenase reaction</p> <p>Mitochondrial oxidative phosphorylation</p> <p>Electron-transfer flavoprotein reaction</p> <p>Hemoglobin auto-oxidation (within erythrocyte)</p> <p>Nitric oxide synthases (NOS)-mediated reaction</p> <p>Eosinophil peroxidase (EPX)-mediated reaction (within eosinophil granulocytes)</p> <p>Myeloperoxidase (MPO)-dependent oxidation (within neutrophil granulocytes)</p>	<p>Mitochondria</p> <p>Cytosol</p> <p>Plasma membrane</p> <p>Peroxisomes</p> <p>Nucleus</p> <p>Endoplasmic reticulum</p> <p>Cytosol</p> <p>Endoplasmic reticulum</p> <p>Lysosome</p>

Table I. Continued.

Reactive oxygen species	Intracellular sources	Compartment
OH-	Fenton reaction	Vacuole
	Haber-Weiss reaction	Plasma membrane
	Hydroperoxide (ROOH) decomposition	Mitochondria
		Nucleus
O ₂ ^{•2-}		Mitochondria
		Cytosol
		Endoplasmic reticulum
		Lysosome
O ₃	Peroxide is unstable molecule. Hydrogen peroxide is more stable molecule formed as described above.	Mitochondria
		Cytosol
		Peroxisomes
		Plasma membrane
NO•		Endosomes
		Endoplasmic reticulum
		Lysosome
		Nucleus
ONOO-	Ozone (O ₃) is unstable molecule generated during antibody catalyzed oxidation of H ₂ O to H ₂ O ₂	Cytosol
	Nitric oxide synthases (NOS)-mediated nitrite (NO ₂ ⁻) reduction	Mitochondria
	Xanthine oxidase (XO) reducing nitrates and nitrites	Cytosol
		Peroxisomes
		Endoplasmic reticulum
		Plasma membrane
		Nucleus
		Mitochondria
	Fenton reaction	Cytosol
	Rapid reaction of singlet oxygen (O ₂) and nitric oxide radical (NO•)	Lysosome
	The reaction of hydrogen peroxide (H ₂ O ₂) with nitrite (NO ₂ ⁻)	Endoplasmic reticulum
		Nucleus
ROO•/RCOO•(Peroxy radical)		Peroxisomes
	Lipid peroxidation chain reactions	Cytosol
	Synthesis of eicosanoids	Plasma membrane
	Hydroperoxide (ROOH) decomposition induced by heat or radiation	Peroxisomes
	ROOH reaction with transition metal ions and other oxidants capable of abstracting hydrogen	Endoplasmic reticulum
		Mitochondria
		Nucleus
		Lysosome

Table I. Continued.

Reactive oxygen species	Intracellular sources	Compartment
HO ₂	Fenton reaction	All membranes Mitochondria Cytosol Endoplasmic reticulum Lysosome Cytosol Plasma membrane Nucleus Endoplasmic reticulum Mitochondria Peroxisomes Lysosome Cytosol Plasma membrane Mitochondria Lysosome Peroxisomes Endoplasmic reticulum Nucleus All membranes Mitochondria Cytosol Peroxisomes Endoplasmic reticulum Peroxisomes Lysosome Vacuole
ROOH/RCOOH	Lipoxygenase-mediated reaction Oxidation of biomolecules, including lipids, proteins and DNA Cyclooxygenase reaction Cytochrome P450 monooxygenase reaction Heme-peroxidase turnover	
R•, RO•, R-S•	Hydroperoxide (ROOH) decomposition induced by heat or radiation ROOH reaction with transition metal ions and other oxidants capable of abstracting hydrogen Lipid peroxidation chain reactions	
CO ₃ •-	The reaction between peroxynitrite and CO ₂ SOD-mediated reaction XO-mediated reaction Metal-ion catalyzed decomposition of HCO ₄ •-	

Major intracellular sources of ROS. O₂, singlet oxygen; OH•, hydroxyl radical; H₂O₂, hydrogen peroxide; O₂•-, superoxide anion; HOCL, HOBr, HOI, HOSCN, hypochlorous acid and associated species; OH-, hydroxyl ion; O₂•²⁻, peroxide; O₃, ozone; NO•, nitric oxide radical; ONOO-, peroxynitrite; ROO•/RCCO•, peroxy radical; HOO•, hydroperoxy radical; ROOH/RCCOOH, organic hydroperoxide; R•, RO• R-S•, Organic radicals; CO₃•-, carbonate radical; SOD, superoxide dismutase; XO, xanthine oxidase; HCO₄•-, peroxymonocarbonate.

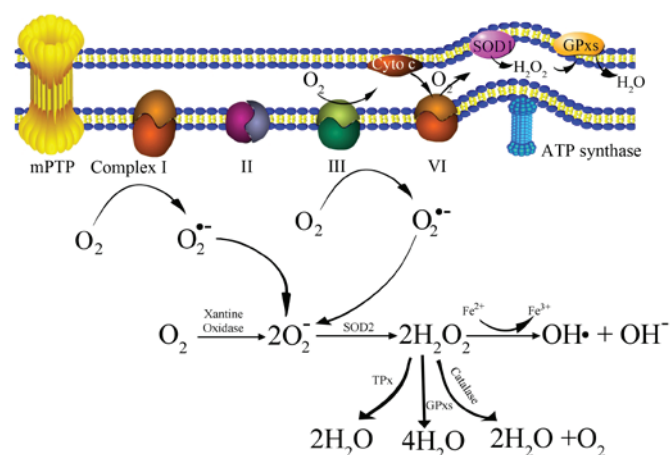


Figure 1. Schematic representation of the generation of mtROS. Complex I, NADH dehydrogenase; II, succinate dehydrogenase; III, bc 1 complex; IV, cytochrome *c* oxidase; V, ATP synthase; Cyto *c*, cytochrome *c*; mPTP, mitochondrial permeability transition pore; SOD, superoxide dismutase; GPxs, glutathione peroxidase; TPx, thioredoxin peroxidase; mtROS, mitochondrial derived reactive oxygen species.

serves a dual role in leukemogenesis. ROS have a pathogenic role in various leukemia models, including CML, MDS and AML (14,52). First, BCR-ABL induces ROS production, which then contributes to malignant transformation, cell growth, resistance to apoptosis and increased DNA damage (53-55). Second, FLT3-ITD mutants induce increased production of ROS, which are responsible for increased DNA double-strand breaks and repair errors (56). Third, activated mutant Ras (N-Ras or H-Ras) induces the production of superoxide and H_2O_2 in human CD34⁺ cells through the stimulation of NOX-1 (NADPH oxidase 1) activity; this effect promotes the growth factor-independent proliferation of these cells (57).

Conversely, ROS and lipid peroxidation by-products are reported to be involved in mitochondria-derived apoptosis and the induction of cell death (6). It has been reported that ROS or lipid peroxidation by-products primarily react to cardiolipin molecules in the inner mitochondrial membrane (IMM), which disturbs the cytochrome *c*-cardiolipin interaction and promotes the release of cytochrome *c* into the cytoplasm, finally resulting in caspase activation and causing cell death (58,59). It has also been demonstrated that HNE reacts with the surrounding molecules near the site of its formation, thereby stimulating chain-reactions of mitochondria-derived apoptosis (60). A recent study explored the molecular mechanisms responsible for the leukemogenesis effect of MLL-AF9 and revealed an essential role of MEIS1 (61). MEIS1 expression in these leukemia types limits the extent of OS and responses for leukemia cell survival, while MEIS1 knockdown in MLL-AF9 leukemic cells induces ROS production and the inhibition of leukemic cell growth. Furthermore, a prior study published by our group demonstrated that increased intracellular ROS levels are important for the induction of cell death and the downregulation of BCR-ABL (62).

Furthermore, ROS participate in numerous cell growth pathways by interfering with the regulation of certain genes and signal transduction pathways, including tumor protein p53 mutation, activator protein-1 (AP-1) activation, vascular endothelial growth factor (VEGF) or rat sarcoma/mitogen

activated protein kinase (Ras/MAPK), nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) signal pathway and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway (63). Ras/MAPK cascades consisting of mitogen-activated protein kinase (ERK1/2), c-Jun N-terminal kinase (JNK), p38 and 14-3-3 β binds to big mitogen-activated protein kinase 1 (BMK1/ERK5) pathways (64) are involved in cytokines and growth factors signaling transmission. The latter, including tumor necrosis factor (TNF)- α , interferon gamma (IFN- γ), epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), bind to their receptors under extracellular or intracellular stimuli and subsequently activate a series of MAP kinases (MAPKKK, MAPKK, MAPK). The activated MAPKs phosphorylate various substrate proteins, resulting in the regulation of various cellular activities (65-67). Each of aforementioned processes may be a target of ROS regulation. For example, it has been demonstrated that ROS activates the receptors of EGF and PDGF without corresponding ligands, thus stimulating Ras and activating the ERK pathway (68,69). Furthermore, in certain cells, treatment with H_2O_2 leads to the phosphorylation and activation of phospholipase C- γ (PLC- γ), and results in the generation of inositol trisphosphate (IP3) and diacylglycerol (DAG). The increase of the IP3 and DAG induces the release of calcium from intracellular stores, and activates numerous forms of Protein Kinase C (PKC), leading to the activation of Ras and Raf and the initiation of ERK signaling (70,71). Akt is a serine/threonine kinase, recruited to the cell membrane by PI3K and activated via phosphorylation. The end result of PI3K/Akt pathway activation is the stimulation of growth pathways and the inhibition of apoptosis, or *vice versa*. ROS not only activate PI3K directly to amplify its downstream signaling, but also concurrently inactivate its negative regulator PTEN (72). For example, it is reported that ROS can induce the phosphorylation of PTEN via casein kinase II, thus urging it to enter the proteolytic degradation pathway (73). ROS influence the NK- κ B pathway mainly through inhibiting I κ B α phosphorylation and degradation, thus activating the NK- κ B pathway. In addition, IKK is the primary target for ROS through S-glutathionylation of the IKK β on cysteine 179, resulting in the inhibition of IKK β activity (74,75).

5. Association between OS and chemotherapy during leukemia treatment

The current therapy for leukemia primarily consists of high-dose cytotoxic chemotherapy with or without allogeneic stem cell transplantation. However, chemotherapeutic treatments are often accompanied by elevated ROS levels, and cause drug-intolerance or resistance correspondingly (75). The underlying mechanisms may be closely associated with the aforementioned ROS-mediated signaling pathway. Chemotherapy impairs the mitotic and metabolic process of cancer cells, involving various signal transmission abnormalities or sub-cellular organ damage, thus causing excess ROS production. Angsutararux *et al* (75) studied doxorubicin (DOX)-induced cardiotoxicity, and proposed that DOX is particularly harmful to the heart due to its exceptional effects on mitochondria, which are the home of ROS. Petrola *et al* (76)

performed a clinical trial to evaluate OS through detecting the levels of MDA and nitrite in patients with CML undergoing treatment with 1st and 2nd generation TKIs. The results indicated that TKIs caused significantly high concentration of ROS in patients CML who were undergoing these treatments, and that oxidative damage markers could indicate resistance to TKIs. Furthermore, it has been demonstrated that anthracyclines, including DOX, a type of important component of current cancer treatment, generate high levels of ROS and cause severe chemotherapy-associated cardiotoxicity (77-79). Therefore, combinations of antioxidants and chemotherapeutic agents perhaps have promising synergistic effects (80). The role of OS in DOX-induced cardiotoxicity can be attenuated in a transgenic mouse model containing high levels of cardiac metallothionein, a potent antioxidant (81). Nakayama *et al* (82) conducted a systematic review of published clinical trials to examine the effects of dietary antioxidants taken concurrently with chemotherapy or radiation therapy. The results indicated that glutathione (GSH), vitamin E and N-acetylcysteine (NAC) were the most frequently used antioxidant supplements in combination with chemotherapy or radiation therapy for kinds of cancer treatments, including leukemia. GSH combined with cisplatin (CDDP)-based chemotherapy accord for 88% of all the experiments (23/26), and adding GSH to CDDP-based chemotherapy could improve the antitumor response against solid tumors and hematological malignancies; some also revealed a neuroprotective effect. Another study reported a trend of longer clinical PFS and OS in patients with CML when they were treated with vitamin A in combination with standard chemotherapy, although this trend was not statistically significant (83).

However, there are conflicting opinions regarding the administration of antioxidants during cancer therapy. Certain researchers suppose that it may reduce the effectiveness of chemotherapies, which are based on increasing oxidative stress. For example, Hewish *et al* (84) revealed that cytarabine was toxic to MLH1 and MLH2 deficient tumor cells, but this cytotoxicity was reduced by antioxidants. In general, the combination of antioxidants and chemotherapy is a promising strategy for cancer treatment, a number of other studies have argued their antagonistic effects. Further studies on the use of this specific combined therapy are required, and further synergistic effects must be investigated and elucidated.

6. Conclusions

Leukemia is a type of hematological neoplasm characterized by the abnormal proliferation and circulation of immature clonal hematopoietic cells in the blood or bone marrow (85). OS has been implicated in leukemogenesis and serves an important role in cell proliferation and cell signaling regulation. Abnormalities in the oxidative-antioxidative balance have been observed in numerous cases of leukemia neoplasm, including ALL, B-CLL and MM.

Indeed, leukemia cells produce higher concentrations of ROS than non-leukemic cells⁸³. OS has beneficial and deleterious effects on leukemogenesis. On the one hand, it promotes leukemia progression through activating oncogenes, including Ras and VEGF, and the NF- κ B signal transduction pathway. Conversely, mitochondria-derived apoptosis can also be induced

by OS and causes cell death. It is difficult to separate the oncogenic properties from the tumor suppressive activity. Therefore, an improved understanding of the association between OS and leukemogenesis will provide more insight for leukemia treatments. Chemotherapy is a commonly used strategy for leukemia treatment. However, the current cytotoxic drugs available for use in standard leukemia therapy are often accompanied by elevated ROS production, and cause drug-intolerance or resistance. Thus, targeting ROS levels during chemotherapy could constitute a novel approach for various types of leukemia, particularly for those of refractory and relapsed hematological neoplasms. Indeed, studies have demonstrated that antioxidant treatments combined with chemotherapy are effective in leukemia therapy, but their concurrent negative effects have also been recorded. Therefore, further studies are required to explore the synergistic effects, long-term effects and consequences of using these combination therapies. Potentially, targeted OS therapy in combination with chemotherapy or other strategies may become a clinically useful therapeutic approach for various types of hematological diseases in the near future.

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Competing interests

The authors declare that they have no competing interests.

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