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

JIN ZHANG[1*], WEN LEI[2*], XIAOHUI CHEN[3], SHIBING WANG[4] and WENBIN QIAN[2]

[1]Department of Hematology, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang 310016; [2]Department of Hematology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003; [3]Department of Hematology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang 310015; [4]Clinical Research Institute, Zhejiang Provincial People's Hospital, Hangzhou, Zhejiang 310014, P.R. China

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.

Correspondence to: Dr Shibing Wang, Clinical Research Institute, Zhejiang Provincial People's Hospital, 158 Shangtang Road, Hangzhou, Zhejiang 310014, P.R. China
E-mail: shibwang@163.com

Professor Wenbin Qian, Department of Hematology, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou, Zhejiang 310003, P.R. China
E-mail: qianwenb@hotmail.com

*Contributed equally

Contents

1. Introduction
2. OS and the generation of ROS
3. Basic ways OS causes cell injury
4. Dual role of OS in leukemogenesis
5. Association between OS and chemotherapy during leukemia treatment
6. Conclusion

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

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

Table I. Major intracellular sources of ROS.

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

Table I. Continued.

Reactive oxygen species	Intracellular sources	Compartment
		Vacuole
		Plasma membrane
		Mitochondria
		Nucleus
OH-	Fenton reaction	Mitochondria
	Haber-Weiss reaction	Cytosol
	Hydroperoxide (ROOH) decomposition	Endoplasmic reticulum
		Lysosome
$O_2^{\bullet 2-}$	Peroxide is unstable molecule. Hydrogen peroxide is more stable molecule formed as described above.	Mitochondria
		Cytosol
		Peroxisomes
		Plasma membrane
		Endosomes
		Endoplasmic reticulum
		Lysosome
		Nucleus
O_3	Ozone (O_3) is unstable molecule generated during antibody catalyzed oxidation of H_2O to H_2O_2	Cytosol
		Mitochondria
$NO\bullet$	Nitric oxide synthases (NOS)-mediated nitrite (NO_2^-) reduction	Cytosol
	Xanthine oxidase (XO) reducing nitrates and nitrites	Peroxisomes
		Endoplasmic reticulum
		Plasma membrane
		Nucleus
ONOO-	Fenton reaction	Mitochondria
	Rapid reaction of singlet oxygen (O_2) and nitric oxide radical ($NO\bullet$)	Cytosol
	The reaction of hydrogen peroxide (H_2O_2) with nitrite (NO_2^-)	Lysosome
		Endoplasmic reticulum
		Nucleus
		Peroxisomes
$ROO\bullet/RCOO\bullet$ (Peroxyl radical)	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
ROOH/RCOOH	Lipoxygenase-mediated reaction Oxidation of biomolecules, including lipids, proteins and DNA Cyclooxygenase reaction Cytochrome P450 monooxygenase reaction Heme-peroxidase turnover	Cytosol Plasma membrane Nucleus Endoplasmic reticulum Mitochondria Peroxisomes Lysosome
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	Cytosol Plasma membrane Mitochondria Lysosome Peroxisomes Endoplasmic reticulum Nucleus
CO3•-	The reaction between peroxynitrite and CO_2 SOD-mediated reaction XO-mediated reaction Metal-ion catalyzed decomposition of HCO_4^-	All membranes Mitochondria Cytosol Peroxisomes Endoplasmic reticulum Peroxisomes Lysosome Vacuole

Major intracellular sources of ROS. O_2, singlet oxygen; OH•, hydroxyl radical; H_2O_2, hydrogen peroxide; O_2•-, superoxide anion; HOCL, HOBr, HOI, HOSCN, hypochlorous acid and associated species; OH-, hydroxyl ion; O_2^{2-}, peroxide; O_3, ozone; NO•, nitric oxide radical; ONOO-, peroxynitrite; ROO•/RCOO•, peroxyl radical; HOO•, hydroperoxy radical; ROOH/RCOOH,organic hydroperoxide; R•; RO•,R-S•, Organic radicals; CO3•-, carbonate radical; SOD, superoxide dismutase; XO, xanthine oxidase; HCO_4^-, peroxymonocarbonate.
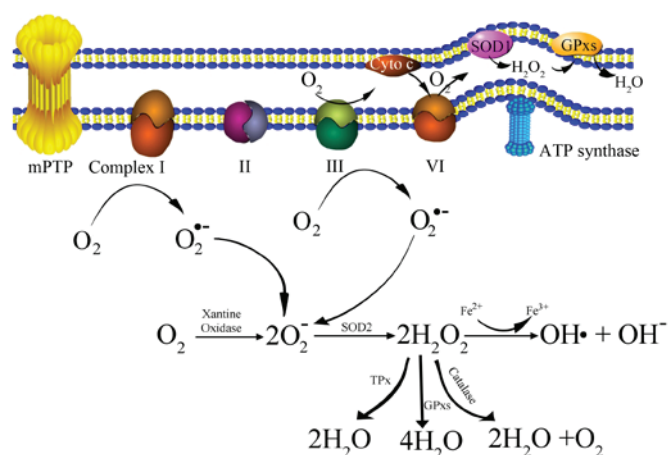
Figure 1. Schematic representation of the generation of mtROS. Complex I, NADH dehydrogenase; II, succinate dehydrogenase; III, bc 1 complex; IV, cytochrome *c* oxidase; V, ATP synthase; Cyto *c*, cytochrome *c*; mPTP, mitochondrial permeability transition pore; SOD, superoxide dismutase; GPxs, glutathione 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-κB) signal pathway and the phosphatidylinositide 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 14-3-3β 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-κB pathway mainly through inhibiting IκBα phosphorylation and degradation, thus activating the NK-κB pathway. In addition, IKK is the primary target for ROS through S-glutathionylation of the IKKβ on cysteine 179, resulting in the inhibition of IKKβ 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-acetysteine (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 cells[83]. 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-κB signal transduction pathway. Conversely, mitochondria-derived apoptosis can olso 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.

Competing interests

The authors declare that they have no competing interests.

References

1. Imbesi S, Musolino C, Allegra A, Saija A, Morabito F, Calapai G and Gangemi S: Oxidative stress in oncohematologic diseases: An update. Expert Rev Hematol 6: 317-325, 2013.
2. Gerschman R, Gilbert D, Nye SW, Dwyer P and Fenn WO: Oxygen poisoning and X-irradiation: A mechanism in common. 1954. Nutrition 17: 162, 2001.
3. Asthana J, Yadav AK, Pant A, Pandey S, Gupta MM and Pandey R: Specioside ameliorates oxidative stress and promotes longevity in Caenorhabditis elegans. Comp Biochem Physiol C Toxicol Pharmacol 169: 25-34, 2015.
4. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M and Telser J: Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39: 44-84, 2007.
5. Weyemi U, Caillou B, Talbot M, Ameziane-El-Hassani R, Lacroix L, Lagent-Chevallier O, Al Ghuzlan A, Roos D, Bidart JM, Virion A, *et al*: Intracellular expression of reactive oxygen species-generating NADPH oxidase NOX4 in normal and cancer thyroid tissues. Endocr Relat Cancer 17: 27-37, 2010.
6. Khoshtabiat L, Mahdavi M, Dehghan G and Rashidi MR: Oxidative stress-induced apoptosis in chronic myelogenous leukemia K562 cells by an active compound from the dithio-carbamate family. Asian Pac J Cancer Prev 17: 4267-4273, 2016.
7. Cheng D, Zhao L, Xu Y, Ou R, Li G, Yang H and Li W: K-Ras promotes the non-small lung cancer cells survival by cooperating with sirtuin 1 and p27 under ROS stimulation. Tumour Biol 36: 7221-7232, 2015.
8. Weyemi U, Lagente-Chevallier O, Boufraqech M, Prenois F, Courtin F, Caillou B, Talbot M, Dardalhon M, Al Ghuzlan A, Bidart JM, *et al*: ROS-generating NADPH oxidase NOX4 is a critical mediator in oncogenic H-Ras-induced DNA damage and subsequent senescence. Oncogene 31: 1117-1129, 2012.

9. Zhu D, Shen Z, Liu J, Chen J, Liu Y, Hu C, Li Z and Li Y: The ROS-mediated activation of STAT-3/VEGF signaling is involved in the 27-hydroxycholesterol-induced angiogenesis in human breast cancer cells. Toxicol Lett 264: 79-86, 2016.
10. Lina M, Hongfei M, Yunxin X, Dai W and Xilin Z: The mechanism of ROS regulation of antibiotic resistance and anti-microbial lethality. Yi Chuan 38: 902-909, 2016.
11. Das DS, Ray A, Das A, Song Y, Tian Z, Oronsky B, Richardson P, Scicinski J, Chauhan D and Anderson KC: A novel hypoxia-selective epigenetic agent RRx-001 triggers apoptosis and overcomes drug resistance in multiple myeloma cells. Leukemia 30: 2187-2197, 2016.
12. Udensi UK and Tchounwou PB: Dual effect of oxidative stress on leukemia cancer induction and treatment. J Exp Clin Cancer Res 33: 106, 2014.
13. Battisti V, Maders LD, Bagatini MD, Santos KF, Spanevello RM, Maldonado PA, Brulé AO, Araújo Mdo C, Schetinger MR and Morsch VM: Measurement of oxidative stress and antioxidant status in acute lymphoblastic leukemia patients. Clin Biochem 41: 511-518, 2008.
14. Chung YJ, Robert C, Gough SM, Rassool FV and Aplan PD: Oxidative stress leads to increased mutation frequency in a murine model of myelodysplastic syndrome. Leuk Res 38: 95-102, 2014.
15. Pawlowska E and Blasiak J: DNA repair-a double-edged sword in the genomic stability of cancer cells-the case of chronic myeloid leukemia. Int J Mol Sci 16: 27535-27549, 2015.
16. Testa U, Labbaye C, Castelli G and Pelosi E: Oxidative stress and hypoxia in normal and leukemic stem cells. Exp Hematol 44: 540-560, 2016.
17. Kudryavtseva AV, Krasnov GS, Dmitriev AA, Alekseev BY, Kardymon OL, Sadritdinova AF, Fedorova MS, Pokrovsky AV, Melnikova NV, Kaprin AD, *et al*: Mitochondrial dysfunction and oxidative stress in aging and cancer. Oncotarget 7: 44879-44905, 2016.
18. Sanganahalli BG, Joshi PG and Joshi NB: Xanthine oxidase, nitric oxide synthase and phospholipase A(2) produce reactive oxygen species via mitochondria. Brain Res 1037: 200-203, 2005.
19. Aprioku JS: Pharmacology of free radicals and the impact of reactive oxygen species on the testis. J Reprod Infertil 14: 158-172, 2013.
20. Murphy MP: How mitochondria produce reactive oxygen species. Biochem J 417: 1-13, 2009.
21. Zhao K, Zeng Q, Bai J, Li J, Xia L, Chen S and Zhou B: Enhanced organic pollutants degradation and electricity production simul-taneously via strengthening the radicals reaction in a novel Fenton-photocatalytic fuel cell system. Water Res 108: 293-300, 2017.
22. Ayala A, Muñoz MF and Argüelles S: Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondi-aldehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev 2014: 360438, 2014.
23. Yin H, Xu L and Porter NA: Free radical lipid peroxidation: Mechanisms and analysis. Chem Rev 111: 5944-5972, 2011.
24. Breitzig M, Bhimineni C, Lockey R and Kolliputi N: 4-Hydroxy-2-nonenal: A critical target in oxidative stress? Am J Physiol Cell Physiol 311: C537-C543, 2016.
25. Negre-Salvayre A, Coatrieux C, Ingueneau C and Salvayre R: Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors. Br J Pharmacol 153: 6-20, 2008.
26. Negre-Salvayre A, Auge N, Ayala V, Basaga H, Boada J, Brenke R, Chapple S, Cohen G, Feher J, Grune T, *et al*: Pathological aspects of lipid peroxidation. Free Radic Res 44: 1125-1171, 2010.
27. Wang G, Wang J, Fan X, Ansari GA and Khan MF: Protein adducts of malondialdehyde and 4-hydroxynonenal contribute to trichloroethene-mediated autoimmunity via activating Th17 cells: Dose- and time-response studies in female MRL+/+ mice. Toxicology 292: 113-122, 2012.
28. Domingues RM, Domingues P, Melo T, Pérez-Sala D, Reis A and Spickett CM: Lipoxidation adducts with peptides and proteins: Deleterious modifications or signaling mechanisms? J Proteomics 92: 110-131, 2013.
29. Stadtman ER and Berlett BS: Reactive oxygen-mediated protein oxidation in aging and disease. Drug Metab Rev 30: 225-243, 1998.
30. Sharma NK, Sethy NK and Bhargava K: Comparative proteome analysis reveals differential regulation of glycolytic and antioxidant enzymes in cortex and hippocampus exposed to short-term hypobaric hypoxia. J Proteomics 79: 277-298, 2013.
31. Chen XL, Zhou L, Yang J, Shen FK, Zhao SP and Wang YL: Hepatocellular carcinoma-associated protein markers inves-tigated by MALDI-TOF MS. Mol Med Rep 3: 589-596, 2010.
32. Hu H, Zhu W, Qin J, Chen M, Gong L, Li L, Liu X, Tao Y, Yin H, Zhou H, *et al*: Acetylation of PGK1 promotes liver cancer cell proliferation and tumorigenesis. Hepatology 65: 515-528, 2017.
33. Ahmad SS, Glatzle J, Bajaeifer K, Bühler S, Lehmann T, Königsrainer I, Vollmer JP, Sipos B, Ahmad SS, Northoff H, *et al*: Phosphoglycerate kinase 1 as a promoter of metastasis in colon cancer. Int J Oncol 43: 586-590, 2013.
34. Singh RK, Tripathi AK, Tripathi P, Singh S, Singh R and Ahmad R: Studies on biomarkers for oxidative stress in patients with chronic myeloid leukemia. Hematol Oncol Stem Cell Ther 2: 285-288, 2009.
35. Rahal ON, Fatfat M, Hankache C, Osman B, Khalife H, Machaca K and Muhtasib HG: Chk1 and DNA-PK mediate TPEN-induced DNA damage in a ROS dependent manner in human colon cancer cells. Cancer Biol Ther 17: 1139-1148, 2016.
36. Chen CY, Yen CY, Wang HR, Yang HP, Tang JY, Huang HW, Hsu SH and Chang HW: Tenuifolide B from cinnamomum tenui-folium stem selectively inhibits proliferation of oral cancer cells via apoptosis, ROS generation, mitochondrial depolarization, and DNA damage. Toxins (Basel) 8: pii: E319, 2016.
37. Kikuchi A, Takeda A, Onodera H, Kimpara T, Hisanaga K, Sato N, Nunomura A, Castellani RJ, Perry G, Smith MA and Itoyama Y: Systemic increase of oxidative nucleic acid damage in Parkinson's disease and multiple system atrophy. Neurobiol Dis 9: 244-248, 2002.
38. Weidner AM, Bradley MA, Beckett TL, Niedowicz DM, Dowling AL, Matveev SV, LeVine H III, Lovell MA and Murphy MP: RNA oxidation adducts 8-OHG and 8-OHA change with Aβ42 levels in late-stage Alzheimer's disease. PLoS One 6: e24930, 2011.
39. Shibutani S, Takeshita M and Grollman AP: Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG. Nature 349: 431-434, 1991.
40. Sunaga N, Kohno T, Shinmura K, Saitoh T, Matsuda T, Saito R and Yokota J: OGG1 protein suppresses G:C->T:A mutation in a shuttle vector containing 8-hydroxyguanine in human cells. Carcinogenesis 22: 1355-1362, 2001.
41. Lovell MA, Soman S and Bradley MA: Oxidatively modified nucleic acids in preclinical Alzheimer's disease (PCAD) brain. Mech Ageing Dev 132: 443-448, 2011.
42. Valavanidis A, Vlachogianni T and Fiotakis C: 8-hydroxy-2'-deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 27: 120-139, 2009.
43. Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, Yanai H and Fraifeld VE: The role of DNA damage and repair in aging through the prism of Koch-like criteria. Ageing Res Rev 12: 661-684, 2013.
44. Fraga CG, Shigenaga MK, Park JW, Degan P and Ames BN: Oxidative damage to DNA during aging: 8-hydroxy-2'-deoxy-guanosine in rat organ DNA and urine. Proc Natl Acad Sci USA 87: 4533-4537, 1990.
45. Chen Q, Fischer A, Reagan JD, Yan LJ and Ames BN: Oxidative DNA damage and senescence of human diploid fibroblast cells. Proc Natl Acad Sci USA 92: 4337-4341, 1995.
46. Vyas P and Jacobsen SE: Clever leukemic stem cells branch out. Cell stem cell 8: 242-244, 2011.
47. Nombela-Arrieta C and Silberstein LE: The science behind the hypoxic niche of hematopoietic stem and progenitors. Hematology Am Soc Hematol Educ Program 2014: 542-547, 2014.
48. Bigarella CL, Liang R and Ghaffari S: Stem cells and the impact of ROS signaling. Development 141: 4206-4218, 2014.
49. Rönn RE, Guibentif C, Saxena S and Woods NB: Reactive oxygen species impair the function of CD90+ hematopoietic progenitors generated from human pluripotent stem cells. Stem cells 35: 197-206, 2017.
50. Cao Y, Fang Y, Cai J, Li X, Xu F, Yuan N, Zhang S and Wang J: ROS functions as an upstream trigger for autophagy to drive hematopoietic stem cell differentiation. Hematology 21: 613-618, 2016.
51. Kaur A, Jankowska K, Pilgrim C, Fraser ST and New EJ: Studies of hematopoietic cell differentiation with a ratiometric and reversible sensor of mitochondrial reactive oxygen species. Antioxid Redox Signal 24: 667-679, 2016.
52. Hole PS, Darley RL and Tonks A: Do reactive oxygen species play a role in myeloid leukemias? Blood 117: 5816-5826, 2011.

53. Sattler M, Verma S, Shrikhande G, Byrne CH, Pride YB, Winkler T, Greenfield EA, Salgia R and Griffin JD: The BCR/ABL tyrosine kinase induces production of reactive oxygen species in hematopoietic cells. J Biol Chem 275: 24273-24278, 2000.
54. Kim JH, Chu SC, Gramlich JL, Pride YB, Babendreier E, Chauhan D, Salgia R, Podar K, Griffin JD and Sattler M: Activation of the PI3K/mTOR pathway by BCR-ABL contributes to increased production of reactive oxygen species. Blood 105: 1717-1723, 2005.
55. Koptyra M, Falinski R, Nowicki MO, Stoklosa T, Majsterek I, Nieborowska-Skorska M, Blasiak J and Skorski T: BCR/ABL kinase induces self-mutagenesis via reactive oxygen species to encode imatinib resistance. Blood 108: 319-327, 2006.
56. Sallmyr A, Fan J, Datta K, Kim KT, Grosu D, Shapiro P, Small D and Rassool F: Internal tandem duplication of FLT3 (FLT3/ITD) induces increased ROS production, DNA damage, and misrepair: Implications for poor prognosis in AML. Blood 111: 3173-3182, 2008.
57. Hole PS, Pearn L, Tonks AJ, James PE, Burnett AK, Darley RL and Tonks A: Ras-induced reactive oxygen species promote growth factor-independent proliferation in human CD34+ hematopoietic progenitor cells. Blood 115: 1238-1246, 2010.
58. Kagan VE, Tyurin VA, Jiang J, Tyurina YY, Ritov VB, Amoscato AA, Osipov AN, Belikova NA, Kapralov AA, Kini V, et al: Cytochrome c acts as a cardiolipin oxygenase required for release of proapoptotic factors. Nat Chem Biol 1: 223-232, 2005.
59. Liu Z, Lin H, Ye S, Liu QY, Meng Z, Zhang CM, Xia Y, Margoliash E, Rao Z and Liu XJ: Remarkably high activities of testicular cytochrome c in destroying reactive oxygen species and in triggering apoptosis. Proc Natl Acad Sci USA 103: 8965-8970, 2006.
60. Zhong H and Yin H: Role of lipid peroxidation derived 4-hydroxynonenal (4-HNE) in cancer: Focusing on mitochondria. Redox Biol 4: 193-199, 2015.
61. Roychoudhury J, Clark JP, Gracia-Maldonado G, Unnisa Z, Wunderlich M, Link KA, Dasgupta N, Aronow B, Huang G, Mulloy JC and Kumar AR: MEIS1 regulates an HLF-oxidative stress axis in MLL-fusion gene leukemia. Blood 125: 2544-2552, 2015.
62. Zhou W, Zhu W, Ma L, Xiao F and Qian W: Proteasome inhibitor MG-132 enhances histone deacetylase inhibitor SAHA-induced cell death of chronic myeloid leukemia cells by an ROS-mediated mechanism and downregulation of the Bcr-Abl fusion protein. Oncol Lett 10: 2899-2904, 2015.
63. Zhang J, Wang X, Vikash V, Ye Q, Wu D, Liu Y and Dong W: ROS and ROS-mediated cellular signaling. Oxid Med Cell Longev 2016: 4350965, 2016.
64. Junttila MR, Li SP and Westermarck J: Phosphatase-mediated crosstalk between MAPK signaling pathways in the regulation of cell survival. FASEB J 22: 954-965, 2008.
65. Pimienta G and Pascual J: Canonical and alternative MAPK signaling. Cell cycle 6: 2628-2632, 2007.
66. Kyriakis JM and Avruch J: Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev 81: 807-869, 2001.
67. Chen Z, Gibson TB, Robinson F, Silvestro L, Pearson G, Xu B, Wright A, Vanderbilt C and Cobb MH: MAP kinases. Chem Rev 101: 2449-2476, 2001.
68. León-Buitimea A, Rodríguez-Fragoso L, Lauer FT, Bowles H, Thompson TA and Burchiel SW: Ethanol-induced oxidative stress is associated with EGF receptor phosphorylation in MCF-10A cells overexpressing CYP2E1. Toxicol Lett 209: 161-165, 2012.
69. Lei H and Kazlauskas A: Growth factors outside of the platelet-derived growth factor (PDGF) family employ reactive oxygen species/Src family kinases to activate PDGF receptor alpha and thereby promote proliferation and survival of cells. J Biol Chem 284: 6329-6336, 2009. .
70. Franklin RA, Atherfold PA and McCubrey JA: Calcium-induced ERK activation in human T lymphocytes occurs via p56(Lck) and CaM-kinase. Mol Immunol 37: 675-683, 2000.
71. Dann SG, Golas J, Miranda M, Shi C, Wu J, Jin G, Rosfjord E, Upeslacis E and Klippel A: p120 catenin is a key effector of a Ras-PKCε oncogenic signaling axis. Oncogene 33: 1385-1394, 2014.
72. Leslie NR and Downes CP: PTEN: The down side of PI 3-kinase signalling. Cell Signal 14: 285-295, 2002.
73. Lee SR, Yang KS, Kwon J, Lee C, Jeong W and Rhee SG: Reversible inactivation of the tumor suppressor PTEN by H2O2. J Biol Chem 277: 20336-20342, 2002.
74. Reynaert NL, van der Vliet A, Guala AS, McGovern T, Hristova M, Pantano C, Heintz NH, Heim J, Ho YS, Matthews DE, et al: Dynamic redox control of NF-kappaB through glutaredoxin-regulated S-glutathionylation of inhibitory kappaB kinase beta. Proc Natl Acad Sci USA 103: 13086-13091, 2006.
75. Angsutararux P, Luanpitpong S and Issaragrisil S: Chemotherapy-induced cardiotoxicity: Overview of the roles of oxidative stress. Oxid Med Cell Longev 2015: 795602, 2015.
76. Petrola MJ, de Castro AJ, Pitombeira MH, Barbosa MC, Quixadá AT, Duarte FB and Gonçalves RP: Serum concentrations of nitrite and malondialdehyde as markers of oxidative stress in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. Rev Bras Hematol Hemoter 34: 352-355, 2012.
77. Cheuk DK, Sieswerda E, van Dalen EC, Postma A and Kremer LC: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer. Cochrane Database Syst Rev: CD008011, 2016.
78. Bartlett JJ, Trivedi PC, Yeung P, Kienesberger PC and Pulinilkunnil T: Doxorubicin impairs cardiomyocyte viability by suppressing transcription factor EB expression and disrupting autophagy. Biochem J 473: 3769-3789, 2016.
79. Piegari E, Russo R, Cappetta D, Esposito G, Urbanek K, Dell'Aversana C, Altucci L, Berrino L, Rossi F and De Angelis A: MicroRNA-34a regulates doxorubicin-induced cardiotoxicity in rat. Oncotarget 7: 62312-62326, 2016.
80. Sabnis HS, Bradley HL, Tripathi S, Yu WM, Tse W, Qu CK and Bunting KD: Synergistic cell death in FLT3-ITD positive acute myeloid leukemia by combined treatment with metformin and 6-benzylthioinosine. Leuk Res 50: 132-140, 2016.
81. Sun X, Zhou Z and Kang YJ: Attenuation of doxorubicin chronic toxicity in metallothionein-overexpressing transgenic mouse heart. Cancer Res 61: 3382-3387, 2001.
82. Nakayama A, Alladin KP, Igbokwe O and White JD: Systematic review: Generating evidence-based guidelines on the concurrent use of dietary antioxidants and chemotherapy or radiotherapy. Cancer Invest 29: 655-667, 2011.
83. Meyskens FL Jr, Kopecky KJ, Appelbaum FR, Balcerzak SP, Samlowski W and Hynes H: Effects of vitamin A on survival in patients with chronic myelogenous leukemia: A SWOG randomized trial. Leuk Res 19: 605-612, 1995.
84. Hewish M, Martin SA, Elliott R, Cunningham D, Lord CJ and Ashworth A: Cytosine-based nucleoside analogs are selectively lethal to DNA mismatch repair-deficient tumour cells by enhancing levels of intracellular oxidative stress. Br J Cancer 108: 983-992, 2013.
85. Kennedy JA and Barabé F: Investigating human leukemogenesis: From cell lines to in vivo models of human leukemia. Leukemia 22: 2029-2040, 2008.