Review

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Chemoprotectants in Cancer Chemotherapy: An Update

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Cancer chemotherapeutic agents play an integral part in the management of patients with malignancy. However, chemotherapy is associated with significant toxicity with an adverse impact on the health of the patients. As a result the therapeutic outcome is influenced due to the inability to deliver sufficient dose-intensive therapy leading to treatment delays or cessation. Chemoprotectants have been developed in order to mitigate the toxicity associated with chemotherapeutic agents by providing organ-specific protection to normal tissues, without compromising the antitumor efficacy. The current review highlights chemoprotectants in the management of chemotherapeutics-associated toxicity, such as: amifostine, aprepitant, dexrazoxane, filgrastim, sargramostim, mesna, oprelvekin, palifermin, recombinant human erythropoietin etc. Additionally, the present status on the concurrent use of chemoprotectants in combination with chemotherapeutic agents, with focus on their safety is included. The advantageous role of these cytoprotective agents combined with chemotherapy remains controversial in clinical studies due to moderate protective efficacy for normal tissues and organs, risk of concomitant tumor protection and adverse reactions. Besides, the number of successful agents is rather small. Therefore, identification of novel approaches and chemoprotectants holds potential for better management of cancer with chemotherapy.

INTRODUCTION

Cytotoxic antineoplastic agents play integral part in the management of cancer patients. However, the chemotherapeutic agents are cytotoxic to the malignant cells, and also affect normal cells (DeVita and Chu, 2008). This results in a narrow therapeutic index coupled with severe form of toxicity impacting adversely on the quality of the life of the patients. Furthermore, the adverse effects result in treatment delays, sub-therapeutic dose delivery and cessation of treatment, and impact the treatment outcome and patient survival (Braun and Seymour, 2011). A summary of common form of chemotherapy-induced toxicities is demonstrated in Table 1.

A better understanding of the cancer

Key words: Chemoprotection, cytoprotective agents, chemotherapy, nutraceuticals, antioxidants, growth factors.
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Table 1: Common form of chemotherapy-induced toxicity.

Types of toxicity	Chemotherapeutic agents		
	Severely toxic	**Moderately toxic**	**Mildly toxic**
Myelotoxicity	Alkylating agents, Anthracyclins, Carboplatin, Cytarabine, Etoposide, Taxanes	Cisplatin, Fluorouracil, Ifosfamide, Methotrexate	Vinca alkaloids
Gastrointestinal toxicity	Anthracyclins	Cytarabine, Etoposide, Fluorouracil, Methotrexate, Nitrosoureas	Alkylating agents, Bleomycin, Cisplatin, Carboplatin, Ifosfamide, Taxanes
Hepatotoxicity		Anthracyclins, Nitrosoureas	Cytarabine, Fluorouracil, Methotrexate, Taxanes
Nephrotoxicity	Cisplatin	Ifosfamide, Methotrexate, Nitrosoureas	Carboplatin
Pulmonary toxicity	Bleomycin	Nitrosoureas	Alkylating agents, Fluorouracil, Ifosfamide, Methotrexate
Peripheral nephropathy	Cisplatin, Taxanes, Vinca alkaloids		Carboplatin
CNS toxicity		Ifosfamide	
Cardiac toxicity	Anthracyclins		Alkylating agents, Fluorouracil, Ifosfamide, Taxanes
Hemorrhagic cystitis	Cyclophosphamide, Ifosfamide		Alkylating agents
Alopecia	Anthracyclins, Etoposide, Taxanes	Alkylating agents, Ifosfamide	Bleomycin, Cytarabine, Nitrosoureas

cell biology was anticipated to identify specific targets for cancer therapy. However, a need for strategies to reduce or circumvent host organ toxicity is the need of the hour (Liu *et al*., 2015). The chemoprotective therapies have been developed to mitigate the healthy tissue toxicity and improve the therapeutic window of cytotoxic antineoplastic agents. Chemoprotection is defined as protection of the toxicity of a chemical through administration of another agent (Jena *et al*., 2010). An ideal chemoprotectant should be easy to administer, non-toxic, not alter the pharmacokinetics of the cytotoxic agent

and should not inhibit or reduce antitumor activity of the drug (Marx and Friedlander, 2010). To cite an example, reactive oxygen species (ROS) generated by anticancer drug or a free radical intermediate of the drug plays a critical role in cytotoxicity of cancer cells, then antioxidative chemoprotectant is not indicated as it will interfere with the antineoplastic activity. However, if generation of ROS is responsible only for the adverse effects of the anticancer drug, then antioxidative chemoprotectant may reduce the severity of the toxicity without interfering with the antineoplastic activity of the drug (Conklin, 2004). The first chemoprotectant in clinical use was folinic acid (calcium folinate; leucovorin), indicated to circumvent methotrexate-induced toxicity (Links and Lewis, 1999).

During chemotherapy, selection of chemotherapeutic agents, and the dose and duration of treatment is dependent on the type and stage of malignancy. However, consideration to selection of appropriate chemoprotectants is often neglected and is equally important (Jena *et al*., 2010). The efficacy of various chemoprotectants differs in terms of potency, pharmacokinetics, accumulation, distribution, and mechanism of action; and hence, these parameters must be taken into account during selection of chemoprotectants for clinical use. It is difficult and perhaps impossible to design a common chemoprotectant to circumvent the deleterious effects, irrespective of individual therapy (chemo or radiation). Thus, the complexity still lies in appropriate selection of chemoprotectants and their use in chemotherapy or radiotherapy without compromising the efficacy. In the current review, currently used chemoprotective agents, their clinical use and limitations have been highlighted.

Amifostine (Ethyol®)

Amifostine (WR-2721, S-2-[3-aminopropylamino] ethylphosphoro-thioic acid) (Fig.1) is a prodrug converted to the active, dephosphorylated, cell permeable metabolite WR-1065 by cell membrane-bound alkaline phosphatase (Hoekman *et al*., 1999), initially used for capability to prevent damage caused by ionizing radiation (Kouvaris *et al*., 2007). It is a broad-spectrum cytoprotectant specific for host organs and tissues and

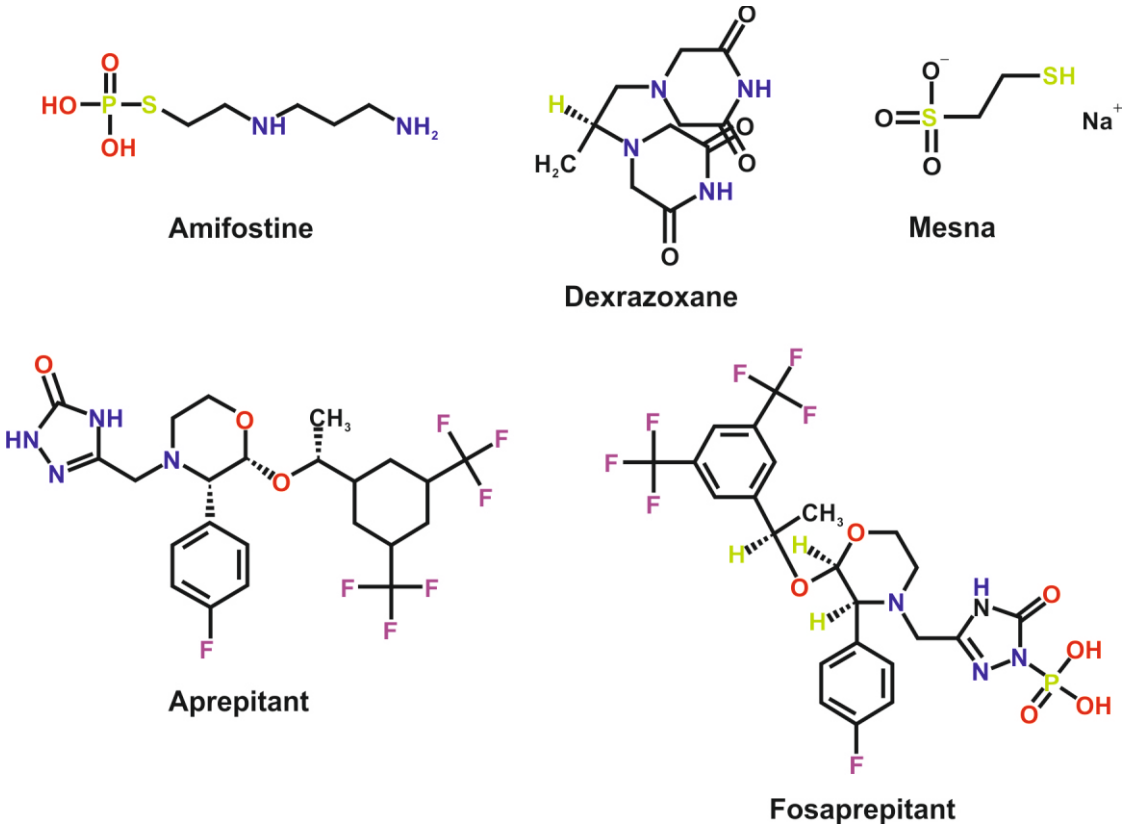


Figure 1: Chemical structure of some clinically used chemoprotectants.

recommended by US Food and Drug Administration (USFDA) for clinical use in patients receiving cisplatin alone and/or in combination with other chemotherapeutic drugs (Ali and Al Moundhri, 2006; Devine and Marignol, 2016). The American Society of Clinical Oncology endorsed amifostine use in prevention of cisplatin-associated nephrotoxicity, for minimization of neutropenia (grade 3–4), and reduce acute and late xerostomia associated with radiotherapy in head and neck cancer (Nicolatou-Galitis *et al*., 2013).

The metabolite of amifostine, WR-1065 is suggested to be responsible for the chemoprotective efficacy of amifostine. Amifostine selectively protects normal organs and tissues due to the greater capillary alkaline phosphatase activity, high pH and superior vascularity of normal tissues in comparison to tumor tissue (van den Berg *et al*., 2006). Thus, normal calls may be able to acquire about 100-fold higher concentration of the free thiol than tumor cells (Marx and Friedlander, 2010). Intracellularly, WR-1065 scavenges free radicals, protecting DNA and cellular membranes from damage (Kouvaris *et al*., 2007). The

oxidation of WR-1065 to WR-33278 (polyamine-like disulfide metabolite) results in higher amount of WR-33278 conjugated DNA, thereby restricting target sites against free radical attack (Savoye *et al*., 1997). Thus WR-1065 contributes to minimization of double-strand breaks following chemotherapy, resulting in recovery of the temporary block of cell cycle at G_2 phase, thereby promoting proliferation of epithelial cells (Rubin *et al*., 1996). Indirectly, amifostine through induction of hypoxia stimulates expression of proteins implicated in DNA repair and inhibition of apoptosis, such as HIF-1α and Bcl-2 (Kouvaris *et al*., 2007).

Amifostine exerts protection as reported in several clinical trials against cisplatin-induced nephrotoxicity and cyclophosphamide-induced hemato-toxicity (Links and Lewis, 1999). The recommended dose for amifostine is 740–910 mg/m^2. Amifostine is well tolerated with the main toxicities being nausea, sneezing, allergic reactions, metallic taste and hypotension. Transient hypocalcaemia has been also noted and is due to the deregulation of parathyroid hormone (Marx and Friedlander, 2010). Clinical trials in advanced ovarian cancer patients confirmed that pre-treatment with amifostine effectively attenuate the cumulative renal, hematologic and neurologic toxicity of the chemotherapy regimen constituting cisplatin and cyclophosphamide (Devine and Marignol, 2016; Kemp *et al*., 1996). Different amifostine analogues have been investigated preclinically to define toxicity. Amongst these, DRDE-07 (S-2 (2-aminoethylamino) ethyl phenyl sulfide) showed most promising efficacy (Gautam *et al*., 2010).

Aprepitant (Emend®)

Chemotherapy-induced nausea and vomiting (CINV) are adverse effects on the quality of life of patients (Ballatori and Roila, 2003). The incidence of CINV influences patient compliance with chemotherapeutic regimens, and influences the decision of patient to undergo chemotherapeutic treatment (Aapro *et al*., 2015). Aprepitant (Fig.1) has emerged as a new class of antiemetic for control of CINV (Grunberg *et al*., 2013). Recent clinical regulations from the Multinational Association for Supportive Care in Cancer (MASCC), European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network

(NCCN) approved aprepitant singly or in combination with serotonin receptor antagonist or corticosteroid, as the most effective therapeutic regimen for reducing both acute and delayed CINV associated with high emetic chemotherapy, or with anthracycline, cyclophosphamide and/or cisplatin-based therapeutic regimens (Aapro *et al*., 2015; Basch *et al*., 2011).

Aprepitant is a highly selective antagonist of human substance P or neurokinin 1 (NK1) receptors. Aprepitant has little or no affinity for dopamine, serotonin (5-HT_3), and corticosteroid receptors, the molecular targets of existing therapies for CINV and postoperative nausea and vomiting (PONV) (Hargreaves *et al*., 2011). Animal and human studies with aprepitant have revealed that by crossing the blood brain barrier it occupies brain NK1 receptors (Bergström *et al*., 2004). Aprepitant augments the antiemetic activity of dexamethasone and 5-HT_3 receptor antagonist ondansetron, and blocks the acute and delayed phases of emesis induced by cisplatin (Di Maio *et al*., 2013). The usual toxicity associated with aprepitant is constipation, tiredness, headache, loss of appetite, and hair loss. In some cases, incidence of pruritus and neutropenia are reported (Aapro *et al*., 2013).

Fosaprepitant (Ivemend®) (Fig.1) is a newly marketed intravenous prodrug formulation of aprepitant. USFDA and European Medicines Agency (EMEA) approved fosaprepitant for prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of moderate to high emetogenic cancer chemotherapy, including high-dose cisplatin (Langford and Chrisp, 2010). Several other NK1 receptor antagonists including casopitant, rolapitant, and netupitant, are undergoing clinical studies for management of CINV (Aapro *et al*., 2015). Casopitant had completed numerous phase III trials, but was not approved by the USFDA because of insufficient safety data (Navari, 2013). Both netupitant and rolapitant were promising in control of CINV. Rolapitant is under phase III trials. Netupitant in combination with palonosetron showed efficiency in reducing CINV in phase III trials (Aapro *et al*., 2014).

Dexrazoxane (Zinecard®)

Dexrazoxane (ICRF-187), a bisdiozpiperazine (Fig.1), is the *d*-isomer of the racemic compound razoxane (ICRF-159) and a lipophilic derivative of

ethylenediaminetetraacetic acid (EDTA), a chelating agent (Hoekman *et al*., 1999). Dexrazoxane has received USFDA approval to minimize the incidence and severity of doxorubicin-associated cardiomayopathy in women with metastatic breast cancer. In UK Dexrazoxane is used for prevention of doxorubicin- or epirubicin-induced chronic cumulative cardiotoxicity in advanced/metastatic cancer patients following anthracycline-therapy (Jones, 2008).

The cardioprotective activity is due to the hydrolysis product ICRF-198 (hydrolyzed by dihydropyrimidine aminohydrolase), which chelates the free and bound forms of myocardial intracellular iron, subsequently decreasing complexation of metal ions with anthracycline, hence leading to a decline in the formation of superoxide anions (Jones, 2008). In addition, dexrazoxane also shows cytotoxic effect via inhibition of topoisomerase II (Zhang *et al*., 2012), and thus potentiates or antagonizes the cytotoxicity of chemotherapeutic agents in experimental tumor models (Hasinoff *et al*., 1998; Sehested *et al*., 1993). Dexrazoxane diminishes doxorubicin-induced cardiotoxicity through its capability to inhibit topoisomerase IIβ (Zhang *et al*., 2012), and degrades topoisomerase IIβ, reducing doxorubicin-induced DNA damage (Lyu *et al*., 2007).

Randomized clinical trials have established the chemoprotective efficacy of dexrazoxane against anthracycline-induced cardiac damage (Doroshow, 2012). Besides, dexrazoxane potentiates hematotoxicity caused by chemotherapy or radiation (Links and Lewis, 1999). The common adverse effects are phlebitis at the site of injection and myelotoxicity (Hoekman *et al*., 1999). Dexrazoxane has been associated with a greater risk of developing secondary malignancy, such as, acute myeloid leukemia and myelodysplastic syndrome in pediatric patients with Hodgkin's disease (Jones, 2008). Recently, dexrazoxane was used as an antidote for anthracycline-induced extravasation injury (Doroshow, 2012).

Filgrastim (Neupogen®) and Sargramostim (Leukine®)

The hematopoietic growth factors (HGFs) are a family of endogenous glycoproteins with a role in survival, proliferation, and differentiation of primordial hematopoietic progenitor and stem cells, and regulation of certain adult cells (Raposo *et al*., 2006). Twenty

molecules of HGF have been characterized, with granulocyte colony-stimulating factor (filgrastim) and granulocyte-macrophage colony-stimulating factor (sargramostim) indicated for reducing febrile neutropenia following chemotherapy and as a supportive therapy in bone marrow transplantation (Mhaskar *et al*., 2014). Filgrastim and sargramostim have been approved for therapy by USFDA on 1991 (Beveridge *et al*., 1998).

Filgrastim is an analog of granulocyte colony-stimulating factor (G-CSF) biosynthesized in *Escherichia coli* by recombinant DNA technology (Sourgens and Lefrère, 2011). Filgrastim stimulates production of neutrophils in the bone marrow, induces proliferation and differentiation of neutrophil progenitor cells, enhances phagocytic ability, antibody dependent killing, priming of the cellular metabolism associated with respiratory burst, and enhances expression of certain cell surface antigens (Haas and Murea, 1995). On the other hand, sargramostim is a yeast-derived recombinant granulocyte macrophage colony-stimulating factor (GM-CSF) (Waller, 2007). During hematopoiesis, sargramostim induces growth of macrophage, granulocyte, lymphocytes and eosinophil colonies (Raposo *et al*., 2006). It generates myeloid dendritic cells and monocytes, leading to greater immunogenic responses, against tumor specific antigens (Waller, 2007). Sargramostim acts on tumor cells by cytokine priming (Boyer *et al*., 2000). In acute myelogenous leukemia (AML), Sargramostim enhances the susceptibility of leukemic blast cells to antitumor activity of chemotherapy. It causes terminal differentiation of cancer stem cells to myeloid cells, thus reducing the number of self-renewing cells (Arellano *et al*., 2007), differentiates the blasts to antigen-presenting cells that activate immune responses and targets the cells for immunotherapy (Boyer *et al*., 2000).

Filgrastim and sargramostim are administered as a prophylactic or curative therapy in patients on myeloablative chemotherapy resulting in prolonged neutropenia. Patients with AML, Hodgkin's lymphoma, non-Hodgkin's lymphoma, sarcomas, seminomas and small cell carcinomas of the lungs are treated with these agents (Raposo *et al*., 2006). Before collection by leukapheresis for hematopoietic stem cell transplantation, Filgrastim is used to augment hematopoietic stem cells in

blood (Kelsey *et al*., 2016). Sargramostim is also indicated in neutropenic patients with myelodysplastic syndrome (MDS) and/or aplastic anemia (Mehta *et al*., 2015). Therapy is usually begun 24–72 hours after cessation of chemotherapy and is often continued until the absolute neutrophil count reaches a normal count of 10,000 cells/µl (Mehta *et al*., 2015). The major associated toxicity includes flu-like symptoms of flushing, rash, fever, malaise, arthralgia, myalgia, headache, anorexia and elevations of serum aminotransferases (Henk *et al*., 2015).

Mesna (Mesnex®)

Mesna (sodium-2-mercapto-ethane sulfonate) (Fig.1) is a specific chemoprotectant against hemorrhagic cystitis induced by cyclophosphamide and ifosfamide (Altayli *et al*., 2012). Cyclophosphamide and ifosfamide undergo biotransformation by hepatic microsomal enzymes to form acrolein and phosphoramide mustard. Acrolein and related urotoxic metabolites, especially 4-hydroxy metabolites (4-hydroxy-ifosfamide and 4-hydroxy-cyclophosphamide) are consequently excreted into the urinary bladder to induce hemorrhagic cystitis (Zhang *et al*., 2006). The incidence of hemorrhagic cystitis following high-dose cyclophosphamide ranges from 0.5-40% in patients (Marx and Friedlander, 2010). Being a thiol compound mesna inactivates alkylating metabolites forming an inert form of thioether. In the bloodstream, mesna is converted to an inactive disulfide form, dithiodiethanesulfate or dimesna. Dimesna is subsequently secreted and filtered in the kidneys, where the enzymes glutathione reductase and thiol transferase reducing dimesna to mesna. Mesna then enters in the bladder, where the free sulfhydryl groups forms a conjugate with acrolein (Links and Lewis, 1999). Mesna also binds to 4-hydroxy-ifosfamide or 4-hydroxy-cyclophosphamide to form a non-urotoxic 4-sulfoethylthio-ifosfamide or 4-sulfoethylthio-cyclophosphamide (Salman *et al*., 2016). As the efficacy of mesna is limited to urinary tract, the non-urological toxicity and the systemic activity of the oxazaphosphorines are not affected. Hence combinatorial treatment with mesna and cyclophosphamide or ifosfamide is effective (Links and Lewis, 1999).

Several clinical studies have

confirmed efficacy of mesna against cyclophosphamide- and ifosfamide-induced bladder toxicity (Salman *et al*., 2016). However, 5% of patients on mesna and cyclophosphamide or ifosfamide therapy suffer from hemorrhagic cystitis during or on completion of the treatment. This may be due to additional metabolites such as chloroethylaziridine and phosphoramide mustard including hemorrhagic cystitis and mesna does not inactivate the agents that cause symptoms of hemorrhagic cystitis (Altayli *et al*., 2012). Mesna minimizes hematuria and hemorrhagic cystitis in patients receiving cyclophosphamide or ifosfamide during chemotherapy (Payne *et al*., 2013). Mesna is also indicated as a mucolytic agent (Sathe *et al*., 2015).

Mesna is generally administered intravenously or orally, with 2 litre of intravenous or oral fluid daily for ensuring hydration. Therapeutic cycles are generally repeated every 3-4 weeks (Links and Lewis, 1999). Mesna is usually associated with minimal toxicity. The most frequently reported adverse effects were headache, dizziness, nausea, vomiting, diarrheal, anorexia, back pain, arthralgia, hyperaesthesia, influenza-like symptoms and coughing (Khaw *et al*., 2007).

Oprelvekin (Neumega®)

Interleukin eleven (IL-11) is a thrombopoietic growth factor that activates proliferation and differentiation of hematopoietic stem cells and megakaryocyte progenitor cells, and induces maturation of megakaryocyte leading to enhanced production of platelet (Cantor *et al*., 2003). Interleukin-11 mRNA extracted from MRC5 human fetal lung fibroblast cell line was used to generate a 178 amino acid encoding cDNA, and biosynthesized in *Escherichia coli*. Oprelvekin is nonglycosylated with a molecular mass of 19kD (Wilde and Faulds, 1998).

Oprelvekin was approved by USFDA for prevention of severe form of thrombocytopenia and in patients with non-myeloid malignancies needing platelet transfusions following myeloablative chemotherapy in patients (Sitaraman and Gewirtz, 2001). Thus it was a pharmacological alternative to platelet transfusions, inducing megakaryocytopoiesis and thrombopoiesis (Adams and Brenner, 1999). The induced platelets are

morphologically and functionally normal with normal life span (Berl and Schwertschlag, 2000). The drug is under investigation for management of inflammatory disorders including rheumatoid arthritis, inflammatory bowel disease, and chemotherapy-associated mucositis (Dorner *et al*., 1997). The non-hematopoietic activity of oprelvekin includes inhibition of adipogenesis, regulation of intestinal epithelium growth, stimulation of osteoclastogenesis and neurogenesis, and inhibition of proinflammatory cytokine production by macrophages (Du and Williams, 1997). However, non-hemopoietic pathological alterations observed in animals include periosteal thickening, fibrosis of tendons and joint capsules, papilledema and embryotoxicity (Smith JW, 2001).

The drug is given subcutaneously, injected in the abdomen, hip or thigh post completion of chemotherapy. Administration must be continued until the platelet count is ≥ 50,000 cells/µl; although administration for more than 21 days is not recommended. Oprelvekin must be discontinued at least 2 days before the subsequent cycle of chemotherapy (Kaye, 1998; Wilde and Faulds, 1998). The drug is not indicated in myelotoxic chemotherapy in pediatric patients as the safety and efficacy have not been established (Cantor *et al*., 2003). The most commonly occurring adverse events are dyspnea, edema, palpitations, tachycardia, pleural effusions, atrial fibrillation/flutter, conjunctivitis and oral moniliasis. Adverse effects include an increase in plasma volume and fluid retention, indicating that oprelvekin should be prescribed with caution in patients with congestive heart failure (Baldo *et al*., 2014).

Palifermin (Kepivance®)

Palifermin is a curtailed derivative of keratinocyte growth factor (KGF or FGF7) produced in *Escherichia coli* using recombinant DNA technology (Finch *et al*., 2013). Palifermin is an aqueous-soluble, 140 amino acid, 16.3 kD protein. The first 23 N-terminal amino acids have been deleted to improve protein stability and thus differ from endogenous human KGF (Baldo *et al*., 2014). Palifermin induces cellular growth responses via FGFR2b receptor, is expressed in oesophagus, buccal mucosa, stomach, salivary gland, intestine, liver, lung, kidney, pancreas, bladder, mammary glands, prostate, lens of the eye, skin and thymus (Vadhan-Raj

et al., 2013). Palifermin shows multiple pharmacological activities such as protection and regeneration of the mucosal epithelium following radiation- and chemotherapy- induced damage. Palifermin causes inhibition of DNA damage and apoptosis of epithelial cells, elevation of detoxifying enzymes and attenuation of pro-inflammatory mediators, along with enhanced proliferation, differentiation and migration of epithelial cells (Blijlevens and Sonis, 2007). Palifermin regulates helper Tcell type1 proinflammatory cytokines and increases helper Tcell type2 antiinflammatory cytokines such as IL4 and IL-13 (Panjwani, 2013).

Clinical use of palifermin to minimize the incidence and duration of severe oral mucositis in patients with hematological malignancies undergoing myeloablative therapy has been recommended by USFDA (Chaveli-López and Bagán-Sebastián, 2016). Palifermin mitigates oral mucositis in patients receiving synchronous chemotherapy/radiotherapy or multi-cycle chemotherapy to treat solid tumors. Efficacy in immune reconstitution after hematopoietic stem cell transplantation and decreasing graft-versus-host disease (GVHD) following allogeneic transplantation is under investigation (Vadhan-Raj *et al*., 2013). Intravenous bolus injection is the recommended route of delivery after myelotoxic chemotherapy (Finch *et al*., 2013).

Palifermin is well tolerated, although side effects such as temporary changes in taste, thickening of buccal mucosa and tongue, white coating of tongue, burning sensation and erythema in skin, pruritus, rash and transient elevation in amylase and lipase have been reported (Vadhan-Raj *et al*., 2013). As palifermin acts as a growth factor for epithelial cells and several carcinomas express FGFR2b, it may potentiate tumor growth, block apoptosis and protect tumor cells from chemotherapy (Baldo *et al*., 2014).

Other Chemoprotective Agents

Besides the chemoprotectants mentioned above, potential clinically relevant chemoprotective agents have been indicated in Table 2. These agents act by interfering with the metabolic and cellular regulatory pathways of chemotherapeutics agents, modifications of inflammatory pathways, and antioxidative mechanisms. Herein, the therapeutic indications, mechanism of action and adverse reactions are tabled (Table 2). Apart from the clinically used

Table 2: Clinically relevant chemoprotective agents

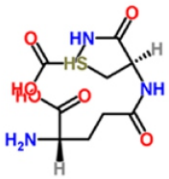
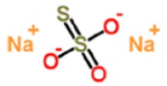
Agents	Therapeutic indication	Mechanism of action	Adverse reactions/ Complications	References
Recombinant human erythropoetin (rhEPO)	Chemotherapy-induced anemia	RhEPO, produced by DNA recombinant technology, stimulates production and maturation of red blood cells. RhEPO acts through its transmembrane receptor (EPO-R). The interaction of ligand and receptor causes activation of JAK2 by transphosphorylation, Src signaling, STAT regulation of genes for cell division and differentiation.	Myalgia, iron deficiency, hypertension, seizures and thromboembolism.	Baldo *et al.*, 2014
Glutathione (γ-glutamine-cysteine-glycine) 	Cisplatin-induced neuropathy, renal and systemic toxicity	Exerts cytoprotective effects. Maintains the active form of glutathione peroxidase for scavenging toxic peroxides. Forms intracellular complexes with cisplatin. Glutathione regulates the kinetics of several ion channels, of importance for the biological integrity of the cell.	Elevated level of glutathione in cancer cells confers resistance to chemotherapeutic agents.	Jena *et al.*, 2010; Traverso *et al.*, 2013
Sodium thiosulfate (STS) 	Cisplatin-induced nephrotoxicity, Chemotherapy-induced extravasation injuries	Neutralizes chemotherapeutic agents by converting them into nontoxic species. Does not interact with intracellular concentration of chemotherapeutic agents.	Arthralgia, blurred vision, hyperreflexia, muscle cramps, nausea and vomiting, psychotic behaviour, tinnitus.	Kreidieh *et al.*, 2016

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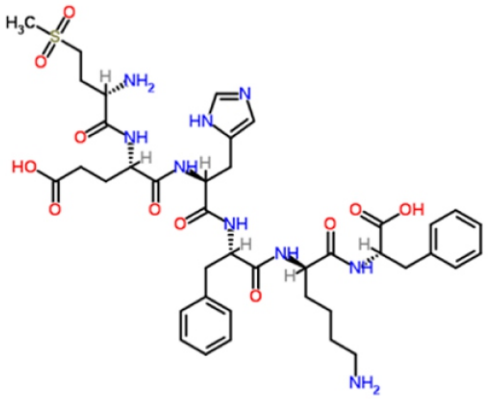
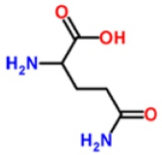
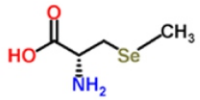
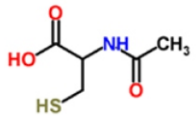
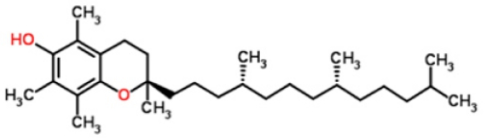
Table 2: Clinically relevant chemoprotective agents (Contd…)

Agents	Therapeutic indication	Mechanism of action	Adverse reactions/ Complications	References
ORG-2766 (Analog of corticotropin) 	Neuropathy induced by Paclitaxel, Vincristine, Cisplatin	Hypothesized that ORG-2766 mimics an endogenous peptide, which stimulates the recovery of damaged neurons.	No significant adverse effects reported	Hershman *et al*., 2014
Glutamine 	Methotrexate-, Fluorouracil-induced gastrointestinal toxicity, Cyclophosphamide-induced systemic toxicity, Anthracycline-induced cardiotoxicity, Taxanes-induced neurotoxicity	Protective role through upregulation of GSH, and induces heat shock protein 72 (HSP 72). As a ‘‘stress response’’ induced in response to cell stressors.	Chest pain, nausea, vomiting, abdominal pain, flatulence, arthralgia, depression and edema.	Gaurav *et al*., 2012
5-Methylselenocysteine (MSC) 	Cisplatin-induced hematological, renal and ototoxicity	MSC induces downregulation of reactive oxygen species (ROS) leading to stabilization of prolylhydroxylase (PHD) 2 and 3 with consequent degradation of HIF-1α. MSC down regulates COX2, and iNOS2.	Mild toxicity in liver and kidneys.	Bhattacharya, 2011

Contd…

Table 2: Clinically relevant chemoprotective agents (Contd…)

Agents	Therapeutic indication	Mechanism of action	Adverse reactions/ Complications	References
N-acetyl-L-cysteine (NAC) 	Cyclophosphamide-, Ifosfamide-induced hemorrhagic cystitis, Cisplatin-induced ototoxicity	Serves as a prodrug to L-cysteine and sulfhydryl groups, and causes reduction of extracellular cystine to cysteine. Stimulates glutathione synthesis, enhances glutathione-*S*-transferase activity, promotes liver detoxification by inhibiting xenobiotic biotransformation, and scavenges free radicals. Possesses anti-inflammatory effects possibly via inhibiting NF-κβ and modulating cytokine synthesis.	Rash, urticaria, pruritus, hypotension, wheezing, and shortness of breath. May accelerate tumor growth by disrupting the ROS-p53 axis apoptosis.	Radomska-Leśniewska and Skopiński, 2012
α-Tocopherol (Vitamin E) 	Chemotherapy-induced systemic toxicity, especially peripheral neuropathy	Vitamin E is a peroxyl radical scavenger, disabling production of damaging free radicals in tissues. Treatment with α-tocopherol downregulated expression of CD36 scavenger receptor gene and scavenger receptor class A (SR-A); and modulates expression of the connective tissue growth factor (CTGF). *CTGF* expression results in repair of wounds and regeneration of extracellular tissues damaged during chemotherapy. Protects lipids and prevents oxidation of polyunsaturated fatty acids.	Nausea, diarrhea, stomach cramps, blurred vision, rash, bruising and bleeding. α-tocopherol may increase the possibility of hemorrhagic stroke in brain.	Nakayama *et al*., 2011

Contd…

Table 2: Clinically relevant chemoprotective agents (Contd…)

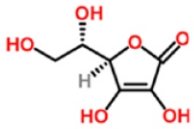
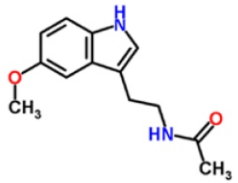
Agents	Therapeutic indication	Mechanism of action	Adverse reactions/ Complications	References
Vitamin C (Ascorbic acid) 	Chemotherapy-related symptoms, such as fatigue, insomnia, loss of appetite, nausea, and pain.	Vitamin C is a potent antioxidant scavenges free radicals and reactive oxygen species. High-dose I.V. vitamin C reduces inflammation, indicated by levels of C-reactive protein (CRP), tumor necrosis factor (TNF-α), interferon-γ (IFN-γ), and the interleukins IL-1, IL2, IL-6, IL-8, in cancer patients.	Indigestion, diarrhea and skin rashes. Vitamin C interferes with antitumor activity of methotrexate, dacarbazine and doxorubicin.	Carr *et al*., 2014
Melatonin (*N*-acetyl-5-methoxy tryptamine) 	Chemotherapy-induced systemic toxicity	Melatonin eliminates free radicals, and also induces production of antioxidant enzymes. Melatonin is immunomodulatory and endocrine-modulatory.	Headaches, dizziness, nausea and drowsiness	Seely *et al*., 2012

Table 3: Promising preclinical chemoprotective compounds.

Compounds	Chemoprotective efficacy	Mechanism of action	References
Epigallocatechin-3-gallate (ECGC)	Cyclophosphamide-induced systemic toxicity and DNA damage	Acts as an antioxidant, reduces lipid peroxidation and genotoxicity	Sai Sampath *et al*., 2011
Selenium nanoparticle (Nano-Se)	Cyclophosphamide-induced hepatotoxicity, pulmonary toxicity and genetic damage	Mitigates oxidative stress, DNA damage and enhances antioxidant status	Bhattacharjee *et al*., 2014; Bhattacharjee *et al*., 2015
Indole-3-carbinol (I3C)	Cyclophosphamide-induced developmental toxicity and teratogenicity	Attenuates limb malformation and tail malformation	Bailey et al., 2005
Resveratol	Doxorubicin-induced cardiotoxicity	Ameliorates activity of Na^+,K^+-ATPase and antioxidant enzymes	Tatlidede *et al*., 2009
Crocin	Doxorubicin-induced myocardial toxicity	Reduces oxidative stress, enhances host anti-oxidant defenses and decreases apoptosis by restoring the balance between proinflammatory (TNF-α, IL-1β and caspase-3) and antiinflammatory (IL-10) cytokines.	Elsherbiny *et al*., 2016
Hesperetin	Doxorubicin-induced testicular toxicity	Prevents oxidative stress, DNA damage and apoptosis by reducing expression of NF-κβ, p38 and caspase-3.	Trivedi *et al*., 2011
Edarabone	Doxorubicin-induced cardiomyopathy	Improves conduction abnormalities, arrhythmia and myocardial ischemia	Xin *et al*., 2011
Diphenylmethyl selenocyanate (DMSE)	Cisplatin-induce nephrotoxicity	Enhances activity of antioxidant enzymes and inhibits expression of proinflammatory COX-2 and *i*NOS.	Chakraborty *et al*., 2011

Contd…

Table 3: Promising preclinical chemoprotective compounds (Contd…)

Compounds	Chemoprotective efficacy	Mechanism of action	References
Erdosteine	Cisplatin-induced renal failure	Modulates function of hexokinase (HK), glucose-6-phosphate dehydrogenase (G6PD), lactate dehydrogenase (LDH) and malate dehydrogenase (MDH)	Yilmaz *et al*., 2004
Vanadium(III)-L-cysteine	Cisplatin-induced nephrotoxicity, myelosuppression and genotoxicity	Restores host redox status, induces Nrf2-mediated ARE pathway and inhibits expression of NFκβ and IL-6.	Basu *et al*., 2015; 2016
Lycopene	Cisplatin-induced nephrotoxicity	Stimulates Nrf2/HO-1 signaling pathway and inhibits NFκβ expression	Sahn *et al*., 2010
Ginseng	Cisplatin-induced nephropathy	Enhances expression of p53 and cJNK followed by reduction in the expression of caspase-3	Park *et al*., 2015
Eicosapentaenoic acid and Docosahexaenoic acid	Cisplatin-induced testicular and spermatological damage	Attenuates oxidative stress by restoring antioxidant defense system	Ciftci *et al*., 2014
Curcumin	Protects normal organs including liver, kidney, oral mucosa, and heart from chemotherapy-induced toxicity	Induces activation of Nrf2 and upregulates expression of antioxidant enzymes. Quenches free radicals and inhibits p300 HAT activity.	Goel and Aggarwal, 2010
Facteur thymique serique (FTS)	Bleomycin-induced pulmonary fibrosis	Suppresses local synthesis of proinflammatory cytokines – TNF-α and IL-1β, chemokines – MCP-1, MIP-1α RANTES, MIP-2 and KC	Yara *et al*., 2001

chemoprotectants there are also some compounds which show promising chemoprotective efficacy in preclinical stages (Table 3).

Conclusion

Evidences in literature validate the potential role of chemoprotectants in the management of toxicities encountered by patients receiving cytotoxic chemotherapeutic drugs. Several of the compounds provide protection without interference with the antitumor activity of the administered antineoplastic agents, and may enable delivery of higher doses of chemotherapeutics. The chemoprotectants in combination with chemotherapeutics is partially effective due to moderate protective efficacy towards normal tissues, potential risk of tumor growth and adverse reactions. The therapy in cancer may have to be directed to develop novel chemoprotective compounds with enhanced specificity to normal cells, with delivery of the drugs not affecting the antitumor efficacy of cytotoxic agents. Development of such selective chemoprotective agents that lessen the burden of treatment and are cost effective is the need of today.

Conflict of Interest

No conflict of interest declaration.

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