

Potential interactions of prescription and over-the-counter medications having antioxidant capabilities with radiation and chemotherapy

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Oncology patients undergoing radiation treatment and chemotherapy routinely use prescription and/or over-the counter medications either as part of pre-existing comorbid conditions or in the context of conventional treatment management. A growing amount of data suggest that commonly used pharmaceuticals possess antioxidant properties, which may also partially explain some of their therapeutic efficacy. Clinical research is continuing on how such agents interact during chemotherapy and radiation when oxidative mechanisms of action are involved. Historically, such discussions centered on the category of dietary supplements, natural health products, fruits and vegetables, along with established protectant medications. Evidence confirms that some pharmaceutical agents exhibit antioxidant properties similar to dietary supplements, protectants, and may hence hinder the efficacy of chemotherapy and radiation treatment. Awareness by both healthcare providers and patients in this area is often lacking. After reviewing some of the more common and well-established pharmaceuticals, which include those prescribed during cancer treatment, caution needs to be advised especially in regards to the use of corticosteroids, as long-term randomized outcome studies ensuring safety in this area are still outstanding.

Antioxidants in the context of oncology primarily comprise dietary supplements, natural health products, and certain fruits and vegetables. For many years, the potential impeding effect of such antioxidants on treatment success and their interaction with various chemotherapeutic agents with suspected oxidative methods of action and in combination with

Key words: antioxidant, chemotherapy, radiation

Abbreviations: ACE: angiotensin-converting enzyme; BAX: BCL-2-associated X protein; BCCAO: bilateral common carotid artery occlusion; BCL-2: B-cell lymphoma-2; COX-2: cyclooxygenase-2; DOX: doxorubicin; 5-FU: 5-fluorouracil; GSH: glutathione; H1 H2: histamine receptors 1,2; LPO: lipid peroxidase; MESNA: 2-mercaptoethane sulfonate Na; MPO: myeloperoxidase; NAC: N-acetylcysteine; NFkB: Nuclear factor kappa beta; NO: nitrogen oxide; NSAID: nonsteroidal anti-inflammatory drug; OH: hydroxyl; PDE-5: phosphodiesterase-5; ROS: reactive oxygen species; SNRI: serotonin and norepinephrine reuptake inhibitor; SOD: superoxide dismutase; SSRI: selective serotonin reuptake inhibitor. This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

DOI: 10.1002/ijc.29208

History: Received 20 May 2014; Accepted 12 Aug 2014; Online 13 Sep 2014

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radiation therapy have been the subject of a controversial discussion within the medical community.^{1–3}

Well-established medications known as protectants, in particular those with reported antioxidant properties, are incorporated into conventional treatment protocols to help preserve cardiac and renal tissues; recommended guidelines are in place.^{4,5} For example, the updated American Society of Clinical Oncology 2008 Clinical Practice Guideline on the use of chemotherapy and radiation therapy protectants states:

“Dexrazoxane is not recommended for routine use in breast cancer in adjuvant setting, or metastatic setting with initial doxorubicin-based chemotherapy. Amifostine may be considered for prevention of cisplatin-associated nephrotoxicity, reduction of grade 3 to 4 neutropenia (alternative strategies are reasonable), and to decrease acute and late xerostomia with fractionated radiation therapy alone for head and neck cancer. It is not recommended for protection against thrombocytopenia, prevention of platinum-associated neurotoxicity or ototoxicity or paclitaxel-associated neuropathy, prevention of radiation therapy-associated mucositis in head and neck cancer, or prevention of esophagitis during concurrent chemoradiotherapy for non-small-cell lung cancer.”

Outside the area of oncology, an increasing number of publications supports the opinion that commonly used pharmaceuticals may provide a therapeutic benefit partially based on their antioxidant properties.^{6–39} Accordingly, oncology patients with co-morbid conditions frequently incorporate such pharmaceuticals into their treatment. In oncology-managed care protocols certain medications are solely prescribed as a direct consequence of the oncologic diagnosis and are incorporated for symptom and therapeutic

management (*i.e.* nausea, insomnia, pain, allergy, etc). Evaluations on how such medications interact with chemotherapy and/or radiation, in particular from an antioxidant perspective, are fragmentary.

Reviewing the vast number of publications in this area of clinical research, there is evidence for concern as some widely used medications may actually possess similar antioxidant capabilities as conventional protectants or dietary supplements and natural health products.^{40,41} The following briefly highlights some prevalent examples for such medications, their mechanisms of interaction and clinical significance.

Carvedilol, a nonselective beta-adrenergic receptor antagonist, protects against cardiac and hepatic mitochondrial bioenergetic dysfunction associated with sub-chronic doxorubicin toxicity.^{42,43} Protective effects of carvedilol against doxorubicin-induced mitochondrial cardiotoxicity, however, are due to its inherent antioxidant activity and not to its beta-adrenergic receptor antagonism. Carvedilol also prevents mitochondrial dysfunction and renal cell death through protection against oxidative stress and redox state unbalances induced by cisplatin.⁴⁴

Captopril, an angiotensin-converting enzyme inhibitor and organosulfur (thiol) compound, protects SA-NH sarcoma cells when present during irradiation. This effect was comparable to amifostine's free thiol WR-1065. When WR-1065, captopril, mesna and *N*-acetyl-cysteine were used 24 h prior to irradiation with 2 Gy, all four thiol-based medications were found to be protective of the cancer.^{45–47}

Morphine inhibits doxorubicin-induced reactive oxygen species generator and nuclear factor kappa beta transcription activation. Morphine showed the same effects as the antioxidant *N*-acetylcysteine on doxorubicin-induced reactive oxygen species generation, caspase-3 activation and mitochondrial cytochrome c release and changes in Bax and Bcl-2 protein expression.⁴⁸

Neuroleptic drugs of the phenothiazine group (*e.g.* chlorpromazine, prochlorperazine, methotrimeprazine) are very powerful scavengers of hydroxyl, peroxy and other radicals (*e.g.* OH·, O₂·⁻, ROO·, ·NO). They inhibit iron ion-dependent liposomal lipid peroxidation.³⁹ The radioprotective effect of chlorpromazine is enhanced significantly in the presence of Fe³⁺.⁴⁹

Glucocorticoids have been shown to decrease xenograft response to paclitaxel through inhibition of tumor cell apoptosis in addition to protecting cardiomyocytes from doxorubicin induced oxidative damage.^{50–52}

In this work we summarily review the literature on prescription and over-the-counter medications with antioxidant properties and those with comparable properties referred to as protectants. A dedicated section describes the role of corticosteroids. Recommendations for the clinical practice are presented.

Protectants, Medications and Mechanisms of Action

The term "antioxidant" is an over-simplification as an agent may act by direct or more complex indirect biochemical

Table 1. Protectants

Protectants	Proposed antioxidant mechanism of action	Refs.
Amifostine	ROS <i>via</i> Thiol (Organosulfur)	57–65
Dexrazoxane	ROS/Iron Chelation	66–69
Mesna/Mesenex/ Uromitexan	ROS <i>via</i> Organosulfur compound	45,70,71

mechanisms. For example, a substance can directly quench the generation of reactive oxygen species, or impede oxidative mechanisms at the cellular level.^{53,54} Indirectly, an agent can trigger or stimulate a cascade of events through the cellular defenses and network.⁵⁵ For example, metformin has been shown to restore the antioxidant profile in human subjects with diabetes mellitus, which includes increasing thiol pools.⁵⁶

Table 1 highlights some commonly used protectants. Table 2 lists a selection of prescription and over-the-counter medications with antioxidant properties and their proposed mechanism of action.

Dexrazoxane has been shown to restore the plasma antioxidant activity assessed *in vitro*, expressed in total oxyradical scavenging capacity, following anthracycline-containing chemotherapy. Dexrazoxane is believed to be protective by preventing oxidative damage *via* its iron chelation properties. Several non-steroidal anti-inflammatory drugs, bisphosphonates, histamine receptor 1,2 antagonists, and phenothiazines possess iron-chelation properties.^{14,75–80,93–95} Celebrex has been shown to both antagonize the cytotoxicity of cisplatin and also protect the kidney against cisplatin-induced nephrotoxicity independent of cyclooxygenase-2 expression.^{76,114}

Protectants containing organosulfur groups (*i.e.* mesna, amifostine) act as potent reducing agents, which easily donate electrons to oxidative elements. As previously stated, captopril, an organosulfur-containing medication with a thiol structure, behaves similarly to amifostine and mesna in response to irradiation.

The Use of Corticosteroids in Oncology

The widespread use of glucocorticoids, which have antioxidant properties, in standard oncology, and in particular in the treatment of solid mass tumors along with chemotherapy and/or radiation is concerning.

The protective effect of glucocorticoids on the tissue of solid tumors has been reported.^{115,116} In particular, Zhang *et al.* have published extensive studies on glucocorticoid-induced resistance in combination with cytotoxic drugs and radiation. They investigated the effect of dexamethasone, prednisone, hydrocortisone and betamethasone in combination with a number of chemotherapeutic agents (cisplatin, etoposide, cytarabine, gemcitabine, methotrexate, 5-fluorouracil, paclitaxel) as well as gamma-radiation and found that 89% of 157 tumor samples analyzed exhibited resistance at clinically

Table 2. Medications

Medication (prescription or over-the-counter)	Proposed antioxidant mechanism of action	Stimulus, chemotherapy, radiation	Study model/tissue type	Outcome	Refs.
ACE inhibitors: organosulfur compounds (captopril); lisinopril	Thiol (similar to protectants); LPO; increasing SOD	2-Gy Irradiation	Human SA-NH Sarcoma (<i>in vitro</i>); Human (hypertensive)	Cancer protective; erythroprotective; cardioprotective	40,72–74
Analgesics: opioids (morphine); acetaminophen; NSAIDs (celecoxib, diclofenac, ibuprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, naprofen, indoprofen, nimesulfide, indomethacin, aspirin)	Iron Chelation and COX inhibition, LPO, OH scavenger	Cisplatin; doxorubicin	Rats	Nephroprotective	48,75–82
Antidiabetics: (metformin); sulfonylureas (glibenclamide)	ROS scavenger, increasing SOD	Doxorubicin	Rat	Cardioprotective; Nephroprotective; Hepatoprotective pancreas—protective	83–88
Antiepileptics (levetiracetam)	NO	Lipopolysaccharide; glutamate	Mouse; rat (<i>in vitro</i>)	Neuroprotective	89–91
Antipsychotics (quetiapine, olanzapine)	ROS scavenger; OH scavenger	Amyloid β (25–35)	Human; mouse	Neuroprotective	35,36
Beta-blockers (carvedilol)	ROS Scavenger	Doxorubicin; cisplatin	Human	Cardioprotective; nephroprotective	6
Bisphosphonates (clodronate, pamidronate, residronate)	Iron chelation; NO	Peroxide	Bovine chondrocytes (<i>in vitro</i>); human leukocytes (<i>in vitro</i>)	Reduced cartilage degradation; antiinflammatory	20,92
Diuretics: thiazides (spironolactone, hydrochlorothiazide)	Thiol (Organosulfur)	n/a	Human (hypertensive)	Renovascular protective	7
H1 blockers (diphenhydramine)	Iron chelation and OH quenching, LPO	Peroxide	Rat liver, brain, gastric mucosa (<i>in vitro</i>)	Hepatoprotective; neuroprotective	93
H2 blockers (cimetidine, famotidine, ranitidine)	Iron Chelation and OH quenching, LPO	Carbon tetrachloride; peroxide	Rat liver and brain (<i>in vitro</i>)	Hepatoprotective; gastroprotective	14,94
Neuroleptics: phenothiazines (chlorpromazine, prochlorperazine, methotrimeprazine); metoclopramide	OH scavenger; ROS scavenger; Iron chelation	Peroxide; hydrochlorous acid; cytochrome c	Rat; various <i>in vitro</i> assays	Hepatoprotective; neuroprotective	39,49,95
Nonbenzodiazepine hypnotics (zolpidem, zopiclone)	ROS scavenger	Peroxide	Rat liver and brain (<i>in vitro</i>)	Neuroprotective	15,96,97

Table 2. Medications (Continued)

Medication (prescription or over-the-counter)	Proposed antioxidant mechanism of action	Stimulus, chemotherapy, radiation	Study model/tissue type	Outcome	Refs.
PDE-5 inhibitors (sildenafil, tadalafil)	Increasing GSH, decreasing MPO and LPO activation, Increasing SOD	Doxorubicin	Mouse	Cardioprotective; nephroprotective	98–100
Proton pump inhibitors (omeprazole, lansoprazole)	OH scavenger	Indomethacin	Rat	Gastroprotective	101
SNRIs (venlafaxine)	NO	BCCAO	Mouse	Protection against ischemia reperfusion induced brain damage, mitochondrial dysfunction	102–104
SSRIs (fluoxetine, sertraline)	ROS Scavenger Increasing SOD	Thioacetamide	Rat (<i>in vitro</i>)	Neuroprotective; hepatoprotective	104,105
Statins (simvastatin, atorvastatin)	ROS Scavenger	Anthracycline	Human (breast cancer)	Cardioprotective; hepatoprotective; renalprotective	12,106–108
Tetracyclic antidepressants (trazodone, mirtazapine)	LPO, NO; increasing SOD	Indomethacin	Rat; mouse (chronic fatigue syndrome)	Neuroprotective; gastroprotective	102,103, 109,110
Tricyclic antidepressants (amitriptyline, desipramine, imipramine)	Increasing SOD	Peroxides	Rat (<i>in vitro</i>)	Neuroprotective	33,102, 104,111
Xanthine oxidase inhibitors (allopurinol)	ROS Scavenger	Carbon tetrachloride, 5-FU	Rat; human colon carcinoma (<i>in vitro</i>)	Hepatoprotective; cancer protective	112,113

Table 3. Protective effect of glucocorticoids on human tumor cells

Cell type or tissue	Treatment	Chemotherapy/radiation	Refs.
Cervix carcinoma	Dexamethasone, prednisone, hydrocortisone, betamethasone	Radiation, cytarabine, cisplatin, gemcitabine, 5-fluorouracil, methotrexate, paclitaxel, etoposide	117,136
Lung cancer	Prednisone; dexamethasone	Gemcitabine, cisplatin	137–139
Glioma, glioblastoma, astrocytoma, medulloblastoma	Dexamethasone	Cisplatin, gemcitabine, staurosporine, temozolomide	117,123,136, 140–142
Breast cancer, ovarian cancer	Dexamethasone	Paclitaxel, cisplatin, 5-fluorouracil, gemcitabine, epirubicin, cyclophosphamide	50,117,118, 134,143,144
Prostate cancer, urological carcinomas	Dexamethasone	Paclitaxel, gemcitabine, cisplatin, 5-fluorouracil, radiation	117,136,145
Hepatocellular carcinoma	Dexamethasone	Cisplatin	117,146
Pancreatic cancer	Dexamethasone	Cisplatin, gemcitabine	117
Melanoma	Dexamethasone	Cisplatin	117
Colorectal tumor cells	Dexamethasone	5-fluorouracil	117
Neuroblastoma	Dexamethasone	Cisplatin, 5-fluorouracil	117
Osteosarcoma	Dexamethasone	Cisplatin	117

achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy.¹¹⁷ Other studies have demonstrated complete blocking effects.¹¹⁸ Furthermore, evidence also suggests that the negative effects of dexamethasone continue up to 1 week following the last administered dose in one study¹¹⁹ and up to several weeks in another.⁵⁰ To our knowledge, these findings have not been validated in human prospective trials for solid mass tumors which includes from an antioxidant perspective.

In humans, glucocorticoids have been correlated with increased metastasis in breast cancer treatment¹²⁰ and worse survival using more than 4 mg of dexamethasone in glioblastoma multiforme at the end of radiation.¹²¹ In contrast, Münstedt *et al.* reported that there was no evidence that glucocorticoid treatment had a negative effect on outcome in patients with ovarian cancer.¹²² The data is preliminary and needs further exploration.

The method of action of glucocorticoids on chemotherapeutic agents and radiation appears complex.^{117,123} In regards to antioxidant capabilities, dexamethasone has been shown to decrease DNA fragmentation caused by oxidative mechanisms¹²⁴ and some data indicates comparable activity to several well-known antioxidant vitamins, which include vitamins A, C, E and coenzyme Q10.^{125–128} Glucocorticoids may increase antioxidant enzymes such as superoxide dismutase due to enzymatic induction mechanisms,¹²⁹ just as reported for amifostine, along with other complex immune system and receptor signaling pathways, which include nuclear factor kappa beta inhibition.^{46,47,130–132}

To our knowledge, the antioxidant potential of dexamethasone has largely been excluded from the discussion on

glucocorticoid-induced chemotherapy and radiation resistance, although, in our opinion, some results reported in the literature could also be explained by antioxidant properties of glucocorticoids.^{133,134}

Adjustments in corticosteroid dosing and frequency have not been explored clinically to assess potential hindrance in patients including those in the neoadjuvant and palliative care setting, where a potential for response may be more easily quantified in the short term. Moreover, there may be a need for dose adjustments at least 1 week prior to receiving chemotherapy and radiation treatment. *In vitro*/animal studies focusing on the timing of incorporating such agents alongside chemotherapy have been conducted,¹³⁵ but again human trials are lacking.

Table 3 lists some of the published literature demonstrating the protective effects of glucocorticoids used with chemotherapy and radiation in various cell and tissue models.

Discussion and Recommendations

Preliminary data suggest that some prescription medications with known antioxidant properties used in patients to treat comorbid conditions may not hinder the efficacy of chemotherapy or radiation treatment and actually augment positive response in some malignancies.¹⁴⁷ For example, patients with diabetes mellitus who are known to present with abnormal or excessive oxidative biomarkers and using the antioxidant medication metformin could be a population group which may be acceptable during chemotherapy and radiation. However, clinical data remain incomplete, and an in depth investigation into the timing/dosing of such medication should be

conducted to assess any potential adverse effect on treatment. Prospective randomized trials would be ideal.

No specific standard exists in assessing antioxidant capabilities. A reliable protocol needs to be created to screen for potential antioxidant-possessing pharmaceuticals used along with reactive oxygen species induced chemotherapy and radiation. Consideration should be given to both *in vitro* and *in vivo* models to examine the broad-based mechanisms that create an antioxidant effect. One proposal suggested the use of known antioxidant-based protectant medications as a comparative standard when developing a test model. Several assays exist to explore the antioxidant capabilities of natural health products and dietary supplements *via* direct and indirect mechanisms.^{148–150} The same should be established for pharmaceutical agents.

All medications and over-the-counter drugs that contain organosulfur compounds in any chemical configuration should generally be viewed as possessing antioxidant capabilities under physiological conditions, especially those with a thiol structure. Iron chelators should be classified in the same category.

All glucocorticoids need to be utilized with the understanding of caution and employed conservatively along with chemotherapy and radiation whenever possible. Alternate strategies should be encouraged.¹⁵¹ For example, Zhang *et al.* reported that unlike glucocorticoids the anti-emetic agents aprepitant and granisetron did not hinder cytotoxic therapy

with cisplatin *in vitro*.¹¹⁷ We are not aware of any reports on potential antioxidant effects of these compounds.

Medications that are new, missed from this review, or have not been evaluated for antioxidant capabilities should be regarded as a potential antioxidants unless proven otherwise.

Conclusion

Physicians are expected to abide by one fundamental principle of medicine—"primum non nocere" or "first, do no harm". In oncology, global efforts are underway to find new and better medicines as well as new protocols and combination treatments with reduced risks and side-effects. It would be unfortunate if it were eventually proven that commonly used supportive medications or those used to assist in comorbid conditions impede an optimal treatment response in the oncology patient while attempting to reach improved life quality and/or enhanced overall survival.

Ultimately, unless clear evidence is available that the benefits of such medications outweigh the potential risk, prescription and over-the-counter medications with established or suspected antioxidant properties should be used with caution and especially if this area continues to be a point of contention by the oncology community. If and when possible considerations which include dose reductions, creative cyclical breaks, or even complete avoidance may be appropriate steps to explore with antioxidant medications used alongside chemotherapy and radiation.

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