The benefits of antioxidants ascorbate and glutathione to protect healthy cells in the prevention and treatment of oncological diseases


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Summary

Health status is determined by balance of oxidants and antioxidants in place to protect healthy cells against the threat of internal and external risk factors. Antioxidants such as ascorbate (vitamin C, ascorbic acid) and glutathione (GSH) are of fundamental importance in this respect. These antioxidants neutralize the potential damage caused by cellular oxidative stress which may be the greatest risk of damage to healthy tissue. Cellular oxidative stress is mediated by external factors (e.g., psychological stress, physical exertion, drugs, various diseases, environmental pollution, preservatives, smoking, and alcohol) and internal factors (products of cellular metabolism including reactive oxygen species). When the products of oxidative stress are not sufficiently neutralized, healthy cells are at risk for both mitochondrial and DNA damage. In the short term, cell function may deteriorate, while sustained increased production of proinflammatory cytokines may lead to the development of chronic inflammatory changes and diseases, including cancer. Although pharmaceutical research continues to bring effective chemotherapy agents to the market, a limiting factor is often the normal tissue and organ toxicity of these substances, which leads to oxidative stress on healthy tissue. There is increasing interest and importance to protect healthy tissues from the negative effects of radio-chemotherapeutic treatment. The action of ascorbate and glutathione against the development of oxidative stress may justify the use of these substances not only in the prevention of carcinogenesis, but as a part of supportive or complementary therapy during treatment. Glutathione and ascorbate (particularly when administered parentally at high doses) may have antioxidant effects that work to protect healthy cells and improving patient tolerability to the some toxic radio-chemotherapy regimens. Ascorbate also has the added demonstrated immunomodulatory effect by supporting mechanisms essential to anti-tumor immunity. In this review, the basic mechanisms and clinical benefits of ascorbate and glutathione as antioxidants that may be useful as supportive therapy to many common chemotherapeutic regimens will be discussed.

Adverse effects of cancer treatments

Despite the progress made by extensive medical and pharmacologic research in the treatment of a wide variety of oncological diseases, a significant limitation of anti-tumor therapy remains the adverse effects. Radiotherapy, for example, causes oxidative stress and is well known to bring local and systemic adverse effects (e.g. myelosuppression). The lack of specificity by numerous treatment methods to impart oxidative stress on diseased cells without similar cytotoxic effects on healthy tissues is precisely what produces the various and often powerful adverse effects (e.g. vomiting, anemia, alopecia, normal tissue necrosis). Even many so-called "targeted therapies" produce adverse effects due to a lack of organ specificity. While these agents may block mechanisms important to pathologic pathways and control disease, they will often simultaneously block normal physiologic processes that commonly lead to many skin and gastrointestinal toxicities.

Published meta-analyses of recent clinical trials for new anti-cancer pharmaceuticals have highlighted the focus on drug efficiency with far less attention on drug toxicity.1,2 In the case of newly registered drugs, increased efficiency and better targeting for treatment may not always bring better patient tolerability; while new drugs are often more effective than existing therapies, they may also have more significant toxicity.1,2 These principles also apply to some targeted drugs. The authors of these meta-analyses conclude that drug approval is still determined primarily by efficacy and argue it is necessary to place more emphasis on their safety.3,4 Potent chemotherapeutic medications may often worsen the quality of life of already debilitated patients resulting in significant morbidity and mortality.

The importance of supportive therapy

The already reduced quality of life of cancer patients may be further impaired by the toxicity of common anti-tumor therapies. Therefore, it may be desirable to supplement this treatment with substances that reduce toxicity and improve patient quality of life. For this purpose, supportive or complementary treatment may be used and has made considerable progress in the last decade. The purpose of supportive treatment is two-fold: first, to alleviate symptoms from the disease itself; and second, to improve symptoms caused by adverse effects of the disease treatment. In this capacity, supportive treatment may be administered prior to radio-chemotherapies as a pre-medication, before the adverse effect but after the treatment has been administered, or as a response to treat side effects after they develop.5 As an example, one very common adverse effect of chemotherapy is nausea and vomiting, which may occur by directly effecting central nervous system control of vomiting. The emetogenic potential of the chemotherapeutic regimen depends on the emetogenic potential of individual drugs comprising the regimen and on the patient’s individual risk factors. Emetogenic treatments can often be supplemented by combination supportive antiemetic prophylaxis. Dopamine receptor blockers (e.g. metoclopramide) and serotonin receptor antagonists (e.g. ondansetron) are commonly used. However, as with any pharmaceutical, the antiemetic therapy has its own set of risks. Dopamine receptor blockers may cause extrapyramidal symptoms and serotonin receptor antagonists have the potential to cause serious arrhythmias. As a result, clinicians must understand the causes of many of the common side effects inflicted on normal tissue by cancer therapies and balance the use of...
these medications with each individual patient’s overall health and co-
morbidities. A solid foundation of understanding can also help clinicians
and researchers develop treatment strategies to diminish normal tissue
toxicity from systemic stress imposed by cancer treatment.

The role of oxidative stress in oncology

Oxidative stress is one fundamentally important mechanism for
unwanted damage to healthy cells during oncological therapy. A classic
example is congestive heart failure secondary to cardiomyopathy cau-
sed by the DNA intercalating agent and anthracycline, doxorubicin. This
anthracycline class of drugs causes formation of free radicals (reactive
oxygen species, ROS) and is responsible for the damage to a variety of
cellular structures. Myocardial tissue may be particularly sensitive to
oxidative stress. To reduce the cardiotoxicity of the anthracycline
cytostatics doxorubicin and epirubicin in patients with breast cancer,
dexrazoxane is used. However, the adverse effects of this medication
must be weighed against the medication risks, most notably the risk of
causing myeloid leukemia and myelodysplastic syndrome. Given these
risks, indications of dexrazoxane were significantly reduced and in many
ways serve as a cautionary tale for complimentary treatment strategies.

It is important to remember that the formation of ROS is a normal
physiological phenomenon in healthy cells. The mitochondria serves
as the main source of ROS but they are also produced by other cellular
structures. Normally, ROS are used in various cell functions such as
signal transduction and phagocytosis. However, ROS production must be
balanced by mechanisms to eliminate excess ROS, including enzym-
atic antioxidant enzymes (e.g. catalases, superoxide dismutases, pe-
roxidases) and non-enzymatic antioxidants such as glutathione (GSH)
and ascorbic acid (vitamin C). The redox environment of the cell is in-
fluenced by the availability of antioxidants, and level of oxidative stress.
Thus, when there is an excess of ROS in a cell either by either increased
production of ROS or decreased concentration of antioxidant enzymes,
oxidative stress occurs. Unless oxidative stress is sufficiently neutralized
by antioxidants, healthy cells may be at risk. Excess ROS causes damage to
cellular protein and DNA and leads to deteriorating cell function and
disease. Oxidative stress on the immune cells weakens anti-tumor de-
fense mechanisms, causes chronic inflammatory changes and has the
potential to lead to cancer.

Important antioxidants essential to the human body to maintain a
general state of health include vitamin C and glutathione. Given the
role played by oxidative stress not only in the origin and development
of cancer, but also for adverse effects caused by toxicity of antitumor
treatment, these drugs have an important place also in supportive treat-
ment to protect healthy cells from disease, prevent side effects of toxic
cancer treatments, and improve overall patient quality of life.

High dose ascorbate

Ascorbate (vitamin C, ascorbic acid) is essential to the human body with
a number of critical physiologic roles. It is a needed cofactor in
multiple enzymatic complexes necessary to synthesize a variety of funda-
mental molecules such as collagen and catecholamines. Additionally,
it is an important antioxidant used to protect healthy tissues against
oxidative stress, a vital role particularly in cancer patients where oxygen
radicals are readily formed as a byproduct of various cancer treatments.
In fact, it is estimated that 30% of cancer patients suffer from a deficien-
cy of vitamin C at diagnosis, likely stemming from a combination of low
dietary intake and increased molecular consumption from the release of
ROS by growing tumor burden. The excess oxidative stress can poten-
tially contribute to further carcinogenesis and to adverse effects from ra-
dio-chemotherapeutic treatments. Cancer patients are increasingly ex-
posed to an oxidative stress feedback loop which promotes malignant
transformation and exposes healthy tissue to the non-selective toxicity
posed by ROS. Not surprisingly, low intake of ascorbate has been found to
increase the incidence of adverse effects associated with chemother-
apy; an effect that is reversed with ascorbate supplementation.

The usage of pharmacologic ascorbate (P-AscH+; High dose intrave-
nous Vitamin C) as a complement to antitumor treatment may be bene-
ificial. Ascorbate functions as a classic antioxidant by readily donating
an electron to potentially harmful ROS. In general, intracellular ascorbate
concentrations are higher than extracellular concentrations and can even
reach millimolar concentrations in circulating neutrophils, lymphocytes,
monocytes, and platelets. Higher levels of intracellular ascorbate are
hypothesized to maintain an intracellular reducing environment that pro-
tects cells from damage caused by ROS created by metabolism, disease,
and ionizing stimuli. Ascorbate is an essential nutrient and humans are
thus entirely dependent on dietary supplies with absorption of ascorba-
tic and dehydroascorbic acid (DHA) by enterocytes in the small intestine.
Ascorbate relies on Na+-dependent vitamin C transporters (SVCTs)
where DHA is absorbed by Na+-independent glucose transporters. Ascor-
bate concentrations are very tightly regulated because of a negative
feedback loop which leads to down-regulation of SVCTs on enterocyte
surfaces in the presence of high intracellular levels. SVCTs are also pre-
sent on renal tubular cells to regulate re-absorption and secretion. As a re-
sult, the bioavailability of orally administered ascorbate is well controlled
at micromolar levels. Systemic plasma millimolar levels can only be
achieved when administered intravenously.

Evidence demonstrating quality of life improvement from compli-
mentary P-AscH+ treatment is beginning to accumulate. In a multicen-
ter, retrospective, cohort in Germany was conducted to evaluate the
safety and efficacy of P-AscH+ in patients with breast cancer. Patients
diagnosed with stage Ila - IIib breast cancer were treated with a 7.5 gram
intravenous dose of P-AscH+ weekly for a minimum of 4 weeks in addi-
tion to standard of care treatment (i.e. chemotherapy, hormone therapy,
and/or radiation). The study found that both during treatment, and du-
ing aftermath, intestinal and neurodegenerative symptoms were decre-
ased in patients receiving P-AscH+. The authors of the study hypothesize
this affect to be directly related to the protective antioxidant capacity of
ascorbate in protecting the gastrointestinal and nervous systems which
are both particularly vulnerable to oxidative stress.

Quality of life (QOL) was also studied by Takahashi and colleagues in
2012.30 Patients with advanced metastatic tumors were given biweekly
P-AscH+ infusions over a four week study period to target blood concen-
trations of 350 – 400 mg/dL immediately following infusion. QOL mea-
sures were tracked prior to treatment, and after two and four weeks of
therapy. Significant increases in QOL measures were noted at both two
weeks and four weeks, including measures of emotional, cognitive and so-
cial function. Other palliative measures were also greatly improved inclu-
ding fatigue, pain, insomnia, constipation, and financial difficulty scores.

P-AscH+ can also play an important role in palliative therapy. QOL
measures were assessed in a prospective study of 39 terminally ill cancer
patients treated with both intravenous and additional oral supplemen-
tation of P-AscH+. The functional scores of patients were found to be
significantly higher with regard to physical, emotional, and cognitive
ability. Symptoms related to fatigue, nausea, vomiting, pain, and appe-
tite loss were also found to be significantly improved.
In addition to its antioxidant effect, which is important for the protection of healthy tissue, ascorbate also plays an important role in maintaining the immune system. The concept of immunological surveillance (tumor immune surveillance) assumes that one of the main roles of the immune system is to eliminate the tumor-transformed cells before they are able to create a tumor mass or metastasis. Ascorbate may be beneficial through a number of mechanisms in regards to antitumor immunity. One mechanism of this effect is to increase the expression of major histocompatibility complex (MHC) class 1 on the surface of tumor cells. The cancer cells defend against attacks by cytotoxic T lymphocytes via inhibiting the surface expression of MHC class 1. Vitamin C increases the expression of this complex on the surface of cancer cells and increases the T lymphocytes ability to recognize the tumor cell and initiate cytotoxic action through cell death signal transduction via Fas and Fas ligand.

Ascorbate also works to suppress IL-18, a cytokine that is produced by some tumor cells in increased amounts and decreases the immune system’s ability to recognize and target tumor cells by suppressing CD70 and upregulating CD44 and VEGF. By suppressing IL-18, ascorbate enhances the effectivity of antitumor immunity against these cancer cells by protecting immune surveillance and inhibiting tumor growth and neovascularization.

Ascorbate supports the adequate function of both humoral and cellular components of the immune system. With respect to cellular immunity, ascorbate primarily supports lymphocyte function, which depends on a sufficiently high intracellular concentration of ascorbate for phagocytosis. Ascorbate also increases the activation and proliferation of natural killer (NK) cells, which are the basic components of nonspecific immunity and tumor surveillance. NK cells are of essential importance not only for its direct cytotoxic effect on tumor cells, but also for their complementary anti-tumor activity with cytotoxic T lymphocytes. Ascorbate’s contribution to antitumor immunity is complex but nevertheless is important to the growing body of knowledge surrounding oncological treatments.

Ascorbate has also been found to reduce inflammation in cancer patients. In fact, proinflammatory cytokines in patients with varying advanced cancers (IL-1α, IL-2, IL-8, TNF-α, chemokine cytokin and CRP) are significantly reduced following P-AscH- treatment. Moreover, in addition to this effect, in-vitro and in-vivo studies detected a selectively cytotoxic effect on some lines of tumor cells treated with P-AscH-.

The effectiveness of P-AscH- in the treatment of pancreatic cancer is related to its ability to act as a prodrug and deliver H2O2 to tumor cells. H2O2 is produced exclusively extracellularly but is easily able to permeate lipid membranes and affect both extracellular and intracellular targets. Extracellularly, H2O2 causes cell membrane damage by forming lipid hydroperoxides with lipid membranes. Intracellularly, H2O2 causes DNA damage and oxidative stress promoting cell death. A significant amount of H2O2 is generated through auto-oxidation when intravenous pharmacologic concentrations are achieved and this reaction is catalyzed in the presence of metal ions.

New mechanisms for the effect of P-AscH- have recently been proposed. Both in-vitro and in vivo that KRAS or BRAF mutant colorectal cancer cells are selectively destroyed by the effects of P-AscH-. Tumor cell death is a result of increased uptake of the oxidized form of vitamin C, dehydroascorbate (DHA), via GLUT1 glucose transporter. The sensitivity of glucose transporter to vitamin C is explained by a high similarity of glucose with vitamin C. As proposed by these investigators, intracellular DHA is then reduced to vitamin C by glutathione, making the cell vulnerable to oxidative stress. As glutathione levels fall, reactive oxygen species accumulate leading to the inhibition glyceroldehyde 3-phosphate dehydrogenase (GAPDH), an important enzyme in glycolysis. A malfunctioning glycolysis system causes an intracellular energetic crisis and eventual tumor cell death. These results have yet to be tested in clinical trials but could offer treatment option to patients with tumors resistant to other treatments in patients with colorectal cancer and pancreatic cancer, where the KRAS mutation is often present.

The effect of vitamin C on chemotherapy and radiotherapy efficacy

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<tr>
<th>Product</th>
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<tr>
<td>5 fluorouracil</td>
<td>↑</td>
<td>Prasad et al., 1979</td>
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<td>Bleomycin</td>
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<td>Prasad et al., 1979</td>
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<td>Doxorubicin</td>
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<td>Kurbacher et al., 1996</td>
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<td>Paclitaxel</td>
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<td>Cisplatin</td>
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<td>Kurbacher et al., 1996</td>
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<tr>
<td>Cyclophosphamide</td>
<td>↑</td>
<td>Reddy et al., 2001</td>
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<td>Procarbazine</td>
<td>↑</td>
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<td>Asparaginase</td>
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<td>Methotrexate</td>
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<td>TRAIL ligand</td>
<td>↑</td>
<td>Perez-Cruz et al., 2007</td>
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<td>Bortezomib</td>
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<td>Zou et al., 2006</td>
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The influence of vitamin C on the antitumor effect of certain chemotherapeutics and radiotherapy has been studied on many tumor types in-vitro and in-vivo. For most of these drugs (e.g. 5 fluorouracil, bleomycin, doxorubicin, paclitaxel, cisplatin, cyclophosphamide, procarbazine, asparaginase, vinblastine, adriamycin, gemcitabine) as well as radiation therapy, an increase in treatment efficacy is seen with the addition of ascorbate. The exception was methotrexate, bortezomib and TNF-related apoptosis-inducing ligand (TRAIL), in which the opposite effect was seen in in-vitro models. A summary of the results of these studies is shown in Table 1.

Clinical safety studies of P-AscH- in combination with chemotherapy With mounting in vitro and in vivo models demonstrating synergistic effects between P-AscH- and chemotherapeutic medications, clinical studies were carried out to determine the safety and efficacy of P-AscH- treatment in humans. These studies have shown the combination of P-AscH- with chemotherapeutics to be safe, with the possibility of a synergistic effect. In a randomized controlled trial in which patients with ovarian cancer treated with combination paclitaxel/carboplatin were also given P-AscH-, the authors found a decrease in the adverse effects of the chemotherapy and an increase in time to relapse compared to
subjects not treated with P-AscH. Phase I of studies of pancreatic cancer patients treated with gemcitabine and/or erlotinib and P-AscH have also shown decreases of tumor mass and a trend of longer survival without any increased risk of toxicity or adverse effects. The clinical data is limited but compelling showing that P-AscH can be administered parallel with standard anti-tumor therapy to improve tolerance to chemotherapy, increase quality of life, and in some cases prolong time to relapse, reduce tumor volume, and prolong survival.

It seems highly plausible that supportive therapy with P-AscH may improve compliance to standard anti-tumor therapies without the risk of additional toxicity. A recent report from the National Cancer Institute of the United States stated P-AscH is safe, well tolerated and has been shown to reduce the adverse effects of basic oncological treatment and improve the quality of life of cancer patients.

Glutathione

Glutathione is the main intracellular antioxidant in the human body. It plays an important role in protecting healthy tissues from oxidative stress and in the elimination of toxic substances (including carcinogens) from the body. The active form of glutathione is its reduced form, referred to as GSH, which has the ability to act as an antioxidant as it reacts with hydrogen peroxide to form the oxidized form (referred to as GSSG). The active, reduced form of glutathione (GSH) is then formed from oxidized (GSSG) through the actions of the enzyme glutathione reductase. Glutathione also contributes to regeneration of ascorbate, thereby further ensuring the protection of cells against oxidative stress.

One important area for glutathione application is oncological disease. Glutathione protects the DNA of healthy cells from damage and thus helps to protect against the negative effects of basic oncological treatment. The protective effect of glutathione’s supplementation on normal tissues is explained by selective penetration of glutathione into the cells. Glutathione preferentially penetrates into non-tumor cells, which are characterized by the normal activity of the enzyme gamma glutamyltransferase. In normal cells, the activity of the enzyme after the exogenous administration of glutathione actually increases, protecting the cell from oxidative stress. Given that absorption is limited with oral administration, it may be beneficial to administer glutathione parenterally.

The protection of healthy cells by glutathione against harmful effects of chemotherapy has been shown in patients treated with cisplatin and oxaliplatin, the drugs from the group of alkylating agents, which cause oxidative stress in the cells (tumor and normal). Studies have also demonstrated the effect of parenterally administered GSH on reducing the nephrotoxicity and neurotoxicity of these agents and improving patient quality of life in patients with ovarian cancer and patients with gastric cancer.

In a study by Smyth and colleagues, GSH was administered intravenously at a dose of 3 g/m² body surface area to a group of patients with ovarian cancer 20 minutes before cisplatin therapy. Compared to controls, the addition of GSH to cisplatin resulted in a significant reduction of nephrotoxicity. In fact, chemotherapy was tolerated by significantly more patients treated by a combination of GSH/cisplatin, allowing for more chemotherapy cycles. GSH also improved the quality of life for patients in regards to depression, hair loss, vomiting, peripheral neurotoxicity, shortness of breath, impaired concentration and common everyday activities. Additionally, combining GSH to cisplatin showed a trend towards higher efficacy of treatment.

In another study, the neuroprotective effects of combination GSH and cisplatin therapy was evaluated in patients with relapsed ovarian cancer. Patients were randomized to receive GSH (2.5 g/m² weekly)/cisplatin or cisplatin alone. The treatment was administered for a period of 9 weeks, after which, patients received a neurologic exam. Neurotoxicity was found to be lower in the group treated with the combination of GSH/cisplatin.

Similar results have also been demonstrated in patients with gastric and colorectal cancer. When tested in gastric cancer patients, the incidence of neurotoxicity after 9 weeks of treatment combining GSH (at 1.5 g/m² weekly) with cisplatin was decreased remarkably. No symptoms of neuropathy were seen in any of the 24 patients receiving the combination of cisplatin with GSH, while in the control group (cisplatin only) the neuropathic symptoms occurred in 16 of 18 patients. In addition, treatment in the group receiving the combination of the GSH/cisplatin was deemed more effective. A double-blind trial was also performed to evaluate the neuroprotective effect of GSH in the chemotherapy regimen of oxaliplatin/leucovorin/5 fluorouracil (FOLFOX) in patients with colorectal cancer. Fifty-two patients were randomized to receive GSH prior to each oxaliplatin administration or to a control group without GSH. The results showed that GSH significantly reduced the neurotoxicity of oxaliplatin, without compromising the efficacy of antitumor treatment. These results were subsequently confirmed by another research group in 2009 in patients receiving FOLFOX4.

Conclusions

Oxidative stress is an important factor in the development of carcinogenesis. Ensuring sufficient levels of antioxidants is therefore an obvious part of cancer prevention. Antioxidants, however, also have an important place in tumor treatment. In cancer patients, healthy tissue may be significantly vulnerable to oxidative stress due to a number of factors and may be exacerbated by radio-chemotherapy regimens. An efficient antioxidant to protect the healthy tissue and increase the quality of life of patients is ascorbate which can be delivered parentally to achieve high doses. At these high levels other benefits have been observed including tumor immunomodulation and, in some cancer cell lines, cytotoxicity. Moreover, ascorbate augments the effectiveness of some chemotherapeutics and radiotherapy. The benefits of P-AscH in combination with certain chemotherapeutic agents has demonstrated safety and efficacy in several clinical studies.

Like ascorbate, glutathione (GSH) represents another important substance providing potential antioxidant protection to healthy tissue. It is a major cellular antioxidant which contributes to the regeneration of ascorbate in the body and protects healthy cells against the toxicity of certain chemotherapeutics that enhance oxidative stress such as cisplatin and oxaliplatin. Clinical studies show the addition of glutathione to the therapeutic regimens containing these drugs reduces the nephrotoxicity and neurotoxicity of treatment. With more clinical studies planned, pharmacological ascorbate and glutathione may become suitable components of supportive therapy for oncological patients.
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