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Review article

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

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Abstract
Health status is determined by the balance of oxidants and antioxidants which protects healthy cells against the threat of internal and external risk factors. Antioxidants such as ascorbate (vitamin C, ascorbic acid) are of fundamental importance in this respect. Ascorbate neutralizes 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 an increased production of proinflammatory cytokines over time may lead to the development of chronic inflammatory changes and diseases, including cancer. Although pharmaceutical research continues to bring effective chemotherapeutic 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 imperative to protect healthy tissues from the negative effects of radio-chemotherapeutic treatment. The action of ascorbate against the development of oxidative stress may justify its use not only in the prevention of carcinogenesis, but as a part of supportive or complementary therapy during treatment. Ascorbate (particularly when administered parentally at high doses) may have antioxidant effects that work to protect healthy cells and improve patient tolerability to some toxic radio-chemotherapy regimens. Additionally, ascorbate has demonstrated an immunomodulatory effect by supporting mechanisms essential to anti-tumor immunity. Intravenous administration of gram doses of vitamin C produce high plasma levels immediately, but the levels drop rapidly. Following oral vitamin C administration, plasma levels increase slowly to relatively low values, and then gradually decay. With an oral liposomal formulation, significantly higher levels are attainable than with standard oral formulations. Therefore, oral administration of liposomal vitamin C appears to be an optimal adjunct to intravenous administration. In this review, the basic mechanisms and clinical benefits of ascorbate as an antioxidant that may be useful as complementary therapy to chemotherapeutic regimens will be discussed.

Keywords: Ascorbic acid; Cancer; Complementary therapy; Intravenous vitamin C; Liposomal vitamin C; Oxidative stress; Vitamin C

Highlights:
- Ensuring sufficient levels of antioxidants is part of cancer prevention.
- Ascorbate neutralizes potential damage caused by cellular oxidative stress which may be the greatest risk of damage to healthy tissue.
- Ascorbate protects oncologic patients' healthy tissues, increases the tolerability to oncologic treatments and increases quality of life.
- Ascorbate exhibits an immunomodulatory effect by supporting mechanisms essential to anti-tumor immunity.
- Pharmacological ascorbate may become suitable component of supportive therapy for oncological patients.
- From a pharmacokinetical point of view, oral administration of liposomal vitamin C appears to be an optimal adjunct to intravenous administration.

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Introduction

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, the adverse effects of anti-tumor therapy remain a significant limitation. 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 often simultaneously block normal physiologic processes which may lead to numerous skin and gastrointestinal toxicities.

Published meta-analyses of recent clinical trials for new anti-cancer pharmaceuticals have highlighted drug efficiency with far less attention paid to drug toxicity (Niraula et al., 2012; 2014). In the case of newly registered drugs, increased efficiency and better targeting for treatment may not always result in improved patient tolerability; while new drugs are often more effective than existing therapies, they may also have more significant toxicity (Niraula et al., 2012; 2014). 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 (Niraula et al., 2012; 2014). Potent chemotherapeutic medications may worsen the quality of life for patients already debilitated, and thus, contributing to significant morbidity and mortality.

The importance of supportive therapy

The 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 natural substances that reduce toxicity and improve patient quality of life. In this regard, supportive or complementary treatment has made considerable progress in the last decade and should be considered. The purpose of supportive treatment is to alleviate symptoms from the disease itself; and 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 effects but after the treatment has been administered; or as a response to treat side effects after they develop (Klener, 2011).

For example, one very common adverse effect of chemotherapy is nausea and vomiting, which may occur by directly affecting the central nervous system's control over 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 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 comorbidities. A solid foundation of understanding can also help clinicians and researchers develop treatment strategies to diminish normal tissue toxicity from systemic stress induced by cancer treatment.

The role of oxidative stress in oncology

Oxidative stress is a fundamentally important mechanism for unwanted damage to healthy cells during oncological therapy. A classic example is congestive heart failure secondary to cardiomyopathy caused by the DNA intercalating agent and anthracycline, doxorubicin (Shakir and Rasul, 2009). The 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 (Chatterjee et al., 2010). To reduce the cardiotoxicity of the anthracycline cytostatics doxorubicin and epirubicin in patients with breast cancer, dexrazoxane is used (Cvetkovic and Scott, 2005; Swain et al., 1997). 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 serve as the main source of ROS, but they are also produced by other cellular structures (Murphy, 2009). 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 enzymatic antioxidant enzymes (e.g. catalases, superoxide dismutases, peroxidases) and non-enzymatic antioxidants, such as ascorbic acid (vitamin C). The redox environment of the cell is influenced by the availability of antioxidants and the level of oxidative stress. Thus, when there is an excess of ROS in a cell either by 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 proteins and DNA and leads to a deterioration of cell function and subsequently, disease. Oxidative stress on the immune cells weakens anti-tumor defense mechanisms, causes chronic inflammatory changes and has the potential to lead to cancer (Klaunig and Kamendulis, 2004).

Antioxidants that are essential to the human body to maintain a general state of health include vitamin C. Given the role that oxidative stress plays in both the origin and development of cancer, but also in the adverse effects caused by toxicity of anti-tumor treatment, this antioxidant has an important place in supportive treatment to protect healthy cells from disease, prevent side effects of toxic cancer treatments, and improve overall patient quality of life.

High dose ascorbate

Ascorbate deficiency, carcinogenesis, tolerance of chemotherapy

Ascorbate (vitamin C, ascorbic acid) is essential to the human body and performs several critical physiological roles. It is a necessary cofactor in multiple enzymatic complexes which synthesize a variety of fundamental 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 vitamin C deficiency at diagnosis, likely stemming from a combination of low dietary intake and increased molecular consumption from the release of ROS by growing tumor burden (Mayland et al., 2005). The excessive oxidative stress can potentially contribute to further carcinogenesis and to adverse effects from radio-chemotherapeutic treatments. Cancer patients are increasingly exposed to an oxidative stress feedback loop which promotes malignant transformation and exposes healthy tissue to the non-selective toxicity posed by ROS (Gupta et al., 2012). Not surprisingly, low intake of ascorbate has been found to increase the incidence of adverse effects associated with chemotherapy; such an effect is reversed with ascorbate supplementation (Kennedy et al., 2004).

Pharmacologic ascorbate: only intravenous administration

The use of pharmacologic ascorbate ($P\text{-}AscH^-$; High dose intravenous Vitamin C) as a complement to anti-tumor treatment may be beneficial (Padayatty et al., 2010). 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 (Levine et al., 1996; Lloyd et al., 1972). Higher levels of intracellular ascorbate are hypothesized to maintain an intracellular reducing environment that protects cells from damage caused by ROS created by metabolism, disease, and ionizing stimuli (Evans et al., 1982; Lane and Lawen, 2009; Li et al., 2012). Ascorbate is an essential nutrient and humans are thus, entirely dependent on dietary sources with absorption of ascorbate and dehydroascorbic acid (DHA) by enterocytes in the small intestine. Ascorbate relies on Na^+-dependent vitamin C transporters (SCVTs) while DHA is absorbed by Na^+-independent glucose transporters (Diliberto et al., 1983; Savini et al., 2008; Vera et al., 1995; Welch et al., 1993). Ascorbate concentrations are tightly regulated via a negative feedback loop which leads to down-regulation of SVCTs on enterocyte surfaces in the presence of high intracellular levels (MacDonald et al., 2002; Padayatty et al., 2004; Savini et al., 2007). SVCTs are also present on renal tubular cells to regulate re-absorption and secretion. As a result, the bioavailability of orally administered ascorbate is well controlled at micromolar levels (Du et al., 2012; Graumlich et al., 1997; Parrow et al., 2013). Systemic plasma millimolar levels can only be achieved when administered intravenously (Parrow et al., 2013). From a pharmacokinetical point of view, intravenous administration of vitamin C is associated with a drawback. Gram level doses can produce immediate plasma levels in the millimole range, but with a half-life of only 0.5 hours, levels drop rapidly. When high doses of vitamin C are administered orally, absorption is incomplete and gradual; plasma levels increase over an hour or two, to a level of about 250 μmol/l, then gradually decay, returning to baseline after approximately six hours. Liposomal formulations of vitamin C greatly increase absorption of the vitamin C, to approximately 90% of an oral dose. Therefore, oral administration of liposomal vitamin C seems to be an optimal adjunct to intravenous administration (Hickey and Roberts, 2013).

High dose ascorbate and quality of life of oncological patients

Evidence demonstrating quality of life improvement from complimentary $P\text{-}AscH^-$ treatment is beginning to accumulate. A multicenter, retrospective study in Germany was conducted to evaluate the safety and efficacy of $P\text{-}AscH^-$ in patients with breast cancer. Patients diagnosed with stage IIa-IIIb breast cancer were treated with a 7.5 gram intravenous dose of $P\text{-}AscH^-$ weekly for a minimum of 4 weeks in addition to standard of care treatment (i.e. chemotherapy, hormone therapy, and/or radiation). The study found that during treatment and during aftercare, intestinal and neurodegenerative symptoms were decreased in patients receiving $P\text{-}AscH^-$. The authors of the study hypothesize this effect to be directly related to the protective antioxidant capacity of ascorbate on the gastrointestinal and nervous systems, both of which are particularly vulnerable to oxidative stress (Vollbracht et al., 2011).

Quality of life (QOL) was also studied in patients with advanced metastatic tumors who were given biweekly $P\text{-}AscH^-$ infusions over a four-week study period to target blood concentrations of 350–400 mg/dl immediately following infusion (Takahashi et al., 2012). QOL measures, including measures of emotional, cognitive and social function, 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. Other palliative measures were greatly improved, including fatigue, pain, insomnia, constipation, and financial difficulty scores.

$P\text{-}AscH^-$ 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 supplementation of $P\text{-}AscH^-$ (Yeom et al., 2007). 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 appetite loss were also found to be significantly improved.

Ascorbate and anti-tumor immunity

In addition to its antioxidant effect, which is important for the protection of healthy tissue, ascorbate 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 (Swann and Smyth, 2007). Ascorbate may be beneficial through a number of mechanisms in regards to anti-tumor immunity (Yu et al., 2011). One mechanism 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 (Yu et al., 2011).

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 (Kang et al., 2009). By suppressing IL-18, ascorbate enhances the effectiveness of anti-tumor immunity against cancer cells by protecting immune surveillance and inhibiting tumor growth and neovascularization (Lee, 2009).

Ascorbate supports the optimal functioning of both humoral and cellular components of the immune system (Holmanová et al., 2012; Lewin, 1976). With respect to cellular immunity, ascorbate primarily supports lymphocyte function, which depends on a sufficiently elevated intracellular concentration of

ascorbate for phagocytosis (Goetzl et al., 1974). Ascorbate also increases the activation and proliferation of natural killer (NK) cells, which are the basic components of nonspecific immunity and tumor surveillance (Dahl and Degré, 1976; Holmannová et al., 2012; Welsh, 1984; Wintergerst et al., 2006). NK cells are quintessential not only for their direct cytotoxic effect on tumor cells, but also for their complementary anti-tumor activity with cytotoxic T lymphocytes (Dahl and Degré, 1976). Ascorbate's contribution to anti-tumor immunity is complex but nevertheless is important to the growing body of knowledge surrounding oncological treatments.

Some other anti-tumor effects of ascorbate

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 eotaxin and CRP) are significantly reduced following P-AscH$^-$ treatment (Mikirova et al., 2012). Moreover *in vitro* and *in vivo* studies detected a selectively cytotoxic effect on some lines of tumor cells treated with P-AscH$^-$ (Du et al., 2010).

The effectiveness of P-AscH$^-$ in the treatment of pancreatic cancer is related to its ability to act as a prodrug and deliver H_2O_2 to tumor cells (Chen et al., 2007). H_2O_2 is produced exclusively extracellularly but is easily able to permeate lipid membranes and affect both extracellular and intracellular targets (Benfeitas et al., 2014; Chen et al., 2005; Wang et al., 1992). Extracellularly, H_2O_2 causes cell membrane damage by forming lipid hydroperoxides with lipid membranes. Intracellularly, H_2O_2 causes DNA damage and oxidative stress promoting cell death (Antunes and Cadenas, 2000). A significant amount of H_2O_2 is generated through auto-oxidation when intravenous pharmacologic concentrations are achieved and this reaction is catalyzed in the presence of metal ions (Frei and Lawson, 2008). A recent study shows that alterations in cancer cell mitochondrial oxidative metabolism resulting in increased levels of $O_2^{\cdot-}$ and H_2O_2 are capable of disrupting intracellular iron metabolism, thereby selectively sensitizing non-small-cell lung cancer (NSCLC) and glioblastoma (GBM) cells to ascorbate through pro-oxidant chemistry involving redox-active labile iron and H_2O_2. Additionally, preclinical studies and clinical trials demonstrate the feasibility, selective toxicity, tolerability, and potential efficacy of pharmacological ascorbate in GBM and NSCLC therapy (Schoenfeld et al., 2017).

New mechanisms for the effect of P-AscH$^-$ have recently been proposed (Yun et al., 2015). Both *in vitro* and *in vivo* studies suggest 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 degree of similarity between glucose and 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 and lead to the inhibition glyceraldehyde 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 a treatment option to patients with treatment-resistant tumors in patients with colorectal cancer and pancreatic cancer, where the *KRAS* mutation is often present (Yun et al., 2015).

The effect of vitamin C on chemotherapy and radiotherapy efficacy

The influence of vitamin C on the anti-tumor effect of certain chemotherapeutics and radiotherapy has been studied on numerous 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 (Gonzales and Miranda-Massari, 2014; Verrax and Calderon, 2008). A summary of the results of some of these studies is shown in Table 1.

Clinical safety studies of P-AscH$^-$ in combination with chemotherapy

With increasing *in vitro* and *in vivo* models demonstrating synergistic effects between P-AscH$^-$ and chemotherapeutic medications, clinical studies were carried out to determine the

Table 1. Effect of vitamin C on the effectiveness of various chemotherapeutic drugs and radiotherapy (taken from Verrax and Calderon, 2008)

Product	Action of vitamin C	Reference
5-fluorouracil	↑a	Prasad et al., 1979
	↑b	Taper et al., 1987
Bleomycin	↑a	Prasad et al., 1979
Doxorubicin	↑a	Kurbacher et al., 1996
Paclitaxel	↑a	Kurbacher et al., 1996
Cisplatin	↑a	Kurbacher et al., 1996
	↑a	Reddy et al., 2001
Cyclophosphamide	↑b	Taper et al., 1987
Procarbazine	↑b	Taper et al., 1987
Asparaginase	↑b	Taper et al., 1987
Vinblastine	↑b	Taper et al., 1987
Adriamycin	↑b	Taper et al., 1987
Gemcitabine	↑b	Kassouf et al., 2006
Vincristine	↑a	Chiang et al., 1994
	↑a	Song et al., 1995
Radiotherapy	↑a	Prasad et al., 1979
	↑b	Taper et al., 1996
Trisenox	↑a	Bahlis et al., 2002
	↑a	Grad et al., 2001
	↑c	Dai et al., 1999
	↓d	Karasavvas et al., 2005
Methotrexate	↓a	Prasad et al., 1979
TRAIL ligand	↓d	Perez-Cruz et al., 2007
Bortezomib	↓a	Zou et al., 2006

a Results *in vitro*
b Results *in vivo* in combination with menadione
c Results *in vivo*
d Results *in vitro* in cells containing ascorbic acid

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 (Ma et al, 2014; Monti et al., 2012; Welsh et al., 2013). In a randomized controlled trial in which ovarian cancer patients treated with a combination of 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$^-$ (Ma et al., 2014). Phase I trials of pancreatic cancer patients treated with gemcitabine and/or erlotinib and P-AscH$^-$ have also shown decreases in tumor mass and a trend of longer survival without any increased risk of toxicity or adverse effects (Monti et al., 2012, Welsh et al., 2013). The clinical data are limited but compelling, showing that P-AscH$^-$ can be administered in 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 (Fritz et al., 2014).

A review paper published in 2015 (Cieslak and Cullen, 2015) examined the use of P-AscH$^-$ in cancer treatment and assessed the current data supporting its potential as an adjuvant in pancreatic cancer. It summarized mechanisms of ascorbate-induced cytotoxicity, and concluded that Phase I trials of pharmacological ascorbate in pancreatic cancer patients have demonstrated safety and potential efficacy of P-AscH$^-$.

A systematic review of use of intravenous ascorbate in cancer clinical trials was published in 2018 (Nauman et al., 2018). Single arm and randomized Phase I/II trials were included in this review, and a total of 23 trials involving 385 patients met the inclusion criteria. One trial (Ma et al., 2014) studied patients suffering from ovarian cancer who were randomized to receive standard chemotherapy with or without intravenous vitamin C (IVC); that trial reported an 8.75 month increase in progression-free survival (PFS) and an improved trend in overall survival (OS) in the vitamin C-treated arm. The authors of the review concluded that, overall, P-AscH$^-$ has been shown to be safe in nearly all patient populations, alone and in combination with chemotherapies, and that the promising results support the need for randomized placebo-controlled trials such as the ongoing placebo-controlled trials of vitamin C and chemotherapy in prostate cancer.

Another paper published in the same year (Klimant et al., 2018) reviews the use of P-AscH$^-$ in cancer care. According to the authors, use of intravenous vitamin C is a safe, supportive intervention to decrease systemic inflammation and to improve symptoms related to antioxidant deficiency, disease processes, and side effects of standard cancer treatments. In doses up to 25 g, IVC can safely be used to treat presumptive ascorbate deficiency and could favourably affect clinical parameters such as inflammation, fatigue, and quality of life. The potential synergy of intravenous vitamin C with chemotherapy or radiation treatment, and the effect on overall outcomes, including survival, of a combined treatment approach, warrant further study according to the authors. Also, future studies examining the effects of IVC in supportive care could add a placebo control in a parallel-arm or crossover design.

Potential mechanisms of action of P-AscH$^-$ in cancer and clinical studies in this field were reviewed in a third 2018 paper (Vissers and Das, 2018). The authors state that there is a substantial body of literature that documents potential anti-tumor effects of ascorbate in *in vitro* and *in vivo* settings, with many reporting cytotoxicity toward cancer cells and a slowing of tumor growth in animal models. As for human clinical studies, most recent Phase I/II studies aiming to determine the tolerability of pharmacological doses of ascorbate for patients with advanced cancer. Some of these studies have suggested that high dose ascorbate treatment may have a clinical benefit for patients with pancreatic cancer (Cieslak and Cullen, 2015; Monti et al., 2012), and other advanced cancers (Hoffer et al., 2015). According to the authors, results of these studies have expanded knowledge of the biological functions of P-AscH$^-$, and, given its lack of toxicity, relative availability, and low cost suggest there is a good rationale to utilize ascorbate as an adjunct treatment for cancer.

It seems highly plausible that supportive therapy with P-AscH$^-$ may improve patient compliance with standard anti-tumor therapies without the risk of additional toxicity. A recent opinion of the National Cancer Institute of the United States stated that P-AscH$^-$ was well tolerated in clinical trials, has been shown to reduce cancer-realted toxicities, and improved the quality of life of cancer patients (National Cancer Institute, 2019).

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 play an important role 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. Several clinical studies have demonstrated the safety and efficacy of P-AscH$^-$ when it is used in combination with certain chemotherapeutic agents. With more clinical studies planned, pharmacological ascorbate may become a suitable component of supportive therapy for oncological patients. From pharmacokinetical viewpoint, oral administration of liposomal vitamin C appears to be an optimal adjunct to intravenous administration.

Conflict of interests

The authors declare no conflict of interests.

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