AIMN review
Australasian Institute for Medical Nutrition
www.aimnutrition.org
MAY 2019

Chemotherapy and Vitamin C

Introduction

Chemotherapy is a first-line medical treatment in cancer, often used in combination with other standard drugs or therapies. There is a growing use of Vitamin C with or around chemotherapy doses that is represented in current research and a long history of the use of Vitamin C in cancer patients in clinical practice. Does vitamin C interfere with chemotherapy, or does it enhance its effects? It turns out that this question is too complex for a one-liner, since what is meant by "chemotherapy" is a complex issue in itself. There are dozens of common drugs being used as chemotherapeutic agents, and of course each of these has a different pharmacodynamic profile and potential interaction with the various dose forms of vitamin C. Data are simply not available on the interactions in a clinical setting with all of these drugs and various doses of vitamin C or other antioxidants. However, the data that are available for many combinations show clearly that the clinical effects of vitamin C co-administered with chemotherapeutic drugs are in fact positive. Recent and emerging clinical research shows that Vitamin C does not interfere with chemotherapy or radiation therapy and that Vitamin C can be used in conjunction with medical therapies to support patient outcomes and improve their quality of life. Vitamin C is not a cure for cancer but clinical research shows it can be a very useful adjunct in treatment.

Current clinical research typically uses high dose intravenous Vitamin C in combination with chemotherapy and radiation therapy. These combinations are not negative interactions and should no longer be considered controversial. This review will look at the current nature and direction of clinical studies and discuss some of the proposed mechanisms for the action of Vitamin C in cancer therapy.

Current clinical trials

Vitamin C and other antioxidants are generic drugs, which means that pharmaceutical companies in general do not pay for or conduct new research into them. Clinical research is expensive and research into combinations of antioxidants and chemotherapy is dependent on grants, which by nature are infrequent and limited. However, a surprising amount of clinical information does exist, both from trials and numerous cases. Add to this a growing list of in-vitro and animal trials and we are seeing a balance of evidence heavily in favour of using antioxidants with chemotherapy. There is currently an explosion of interest in research looking at combinations of Vitamin C with chemotherapy and/or radiotherapy. There are also several current trials where Vitamin C is being used as a sole treatment. A quick glance at registered clinical trials on clinicaltrials.gov will show the extent of the current research.

Registered trials – clinicaltrials.gov

A search of clinicatrials.gov for studies involving Vitamin C and cancer returns in excess of 100 results ("Vitamin C - Cancer - ClinicalTrials.gov," n.d.). Limiting this to intravenous Vitamin C currently produces 40 results. The lists of registered trials are dynamic so it is worthwhile to check in on it and get the latest updates from time to time. Not all of these studies are active, some are terminated and some are completed without published results yet. However, the majority of trials are recruiting or running.

Current research trends

- Several Phase II (the studies are getting larger).
- Vitamin C as a high dose treatment is typically given intravenously. There are a few studies with Vitamin C as a sole treatment. In some cases, Vitamin C is given orally, in same cases it is given both intravenously and orally.
- Vitamin C is typically given with chemotherapy, often on the same day. Often multiple chemotherapy drugs in the same study.
- Completely new – human research on Vitamin C with radiation, Vitamin C is given intravenously in high dose concurrent with radiation.
- Broader range of cancers than previously.

The acceptance by ethics bodies and escalation of current trials into Phases II and III demonstrates that Vitamin C is safe and is not interfering with medical treatments.

Just looking at intravenous Vitamin C in current research, the studies broadly fall into these categories:

With chemotherapy

These studies are using a wide range of drugs and drug classes, often multiple chemotherapy drugs are being trialed at the same time.

Currently 20 studies are listed.

For example:

- **High Dose Ascorbic Acid and Nanoparticle Paclitaxel Protein Bound and Cisplatin and Gemcitabine (AA NABPLAGEM) in Patients Who Have Metastatic Pancreatic Cancer** ("ClinicalTrials.gov Identifier: NCT03908333," 2019)
  - Multi centre, Phase I & II. IVC 25, 37.5, 56.25 or 75 grams/m² with Paclitaxel, Cisplatin and Gemcitabine.

- **Vitamin C and Tyrosine Kinase Inhibitor in Lung Cancer Patients With Epidermal Growth Factor Receptor Mutations** ("ClinicalTrials.gov Identifier: NCT03799094," 2019)
  - Clifford hospital, Guangzhou, China. Randomised controlled, Phase I & II. IVC 30 g / dose, once a week in combination with daily taking tyrosine kinase inhibitor.

Sole treatment

Currently 11 studies are listed. Vitamin C is typically given in high dose, these have sometimes been quality of life (QOL) trials.

For example:

- **The Effect of Vitamin C on Quality of Life of Terminal Cancer Patients** ("ClinicalTrials.gov Identifier: NCT03224572," 2017)
  - Single centre, Taiwan. Parallel Assignment Randomized double-blinded controlled trial. High-dose vitamin C 30 gm in 500 ml normal saline, once per week, and total 4-week treatment or saline same schedule.

- **Therapeutic Use of Intravenous Vitamin C in Allogeneic Stem Cell Transplant Recipients** ("ClinicalTrials.gov Identifier: NCT03613727," 2018)
  - Single centre, USA. Open label, Phase II. The treatment is IV vitamin C 50 mg/kg/day. After completion of the IV vitamin C doses, oral vitamin C 500 mg twice each day.

> *"Numerous Quality of Life (QOL) studies have been conducted looking at the effects of Vitamin C in cancer."*

With radiation therapy

Currently 4 studies are listed. Vitamin C is typically given in high dose, it can be before, during and after radiation. These studies are also typically combination chemotherapy and radiotherapy.

For example:

- **A Phase 2 Study Adding Ascorbate to Chemotherapy and Radiation Therapy for NSCLC (XACT-LUNG)** ("ClinicalTrials.gov Identifier: NCT02905591," 2016)
  - Single centre, USA. Phase II Open label. Radiation therapy, intravenous paclitaxel, intravenous carboplatin, intravenous ascorbic acid (pharmacological ascorbate).
    - 75 grams per infusion; each infusion is about 2 hours
    - 3 infusion per calendar week
    - The infusion is actively running for at least 20 minutes when radiation begins
    - May be given while chemotherapy is delayed due to low counts
    - Dose reductions are not used
    - Given for 6 to 7 weeks, depending on when radiation starts

- **A Phase 2 Trial of High-Dose Ascorbate in Glioblastoma Multiforme** ("ClinicalTrials.gov Identifier: NCT02344355," 2015)
  - Single centre, USA. Phase II Open label. Concomitant therapy: Radiation therapy, oral temozolomide, and pharmacological ascorbate (ascorbic acid) infusions. Adjuvant therapy: Oral temozolomide and pharmacological ascorbate (ascorbic acid) infusions. Intravenous infusions of 87.5g of ascorbate administered three times weekly during radiation. After radiation, ascorbate is administered twice weekly through the end of cycle 6 of temozolomide.

Quality of life trials

Numerous Quality of Life (QOL) studies have been conducted looking at the effects of Vitamin C in cancer. The general overview about the use of Vitamin C in cancer patients is that high dose Vitamin C therapy improves QOL. Patients are often treated with toxic drugs, or combinations of toxic drugs and radiation. While successful, treatment can lead to significant toxicity, dose limiting toxicity, or the requirement for treatment to be stopped due to side effects of treatment. Clinical trials and cases are consistently showing that high dose Vitamin C therapy along with standard medical treatments can in many cases limit toxicity, allowing continuation of therapy, continuation of a higher dose or a general reduction of side effects and improvement in QOL for these patients. Clinical trials have not demonstrated that Vitamin C interferes with chemotherapy or radiotherapy.

In 1976 Cameron and Pauling used high dose Vitamin C (a typical IVC dose was 10g) and oral Vitamin C in cancer patients. They found a dramatic increase in survival compared to matched controls and also found that Vitamin C improved the QOL for these patients (Cameron and Pauling, 1976). It was this study that really set the ball rolling for Vitamin C in clinical research in cancer. Refuting studies using oral Vitamin C followed (Creagan et al., 1979; Moertel et al., 1985) but eventually it was accepted by many researchers and clinicians that Vitamin C needed to be given intravenously to sustain higher blood levels to have the dramatic effect (Duconge et al., 2008).

More formal QOL trials got underway from about 2007 using standard QOL questionnaires such as the EORTC QLQ-30 (European Organisation for Research and Treatment in Cancer). A Korean study in 2007 used 10 g IVC in 2 doses 3 days apart in cancer patients and measured the change in QOL with the EORTC questionnaire (Yeom et al., 2007). They found a significant improvement in QOL in multiple function and symptom scales. This propelled interest in studying the effects of Vitamin C on QOL in cancer patients. A larger German study was published in 2011 (Vollbracht et al., 2011). They looked at the effect of 7.5 g of intravenous Vitamin C weekly on the QOL of cancer patients receiving standard tumor therapy and aftercare. The intensity score for symptoms was close to twice as high in the placebo group compared to the IVC group.

A study in 2012 used a high dose protocol in cancer patients and looked at the effects on QOL using the EORTC questionnaire (Takahashi et al., 2012). The study was conducted in multiple centres in Japan and saw dramatic increases in overall EORTC QOL scores in a group of 60 patients after 2 and 4 weeks of IVC treatment; approximately 140 g of IVC per week. Another QOL study was conducted in China in 2017 (Ou et al., 2017). This was a pharmacokinetic and QOL study using the EORTC questionnaire on patients receiving electro-hyperthermia along with high dose IVC for advanced non-small cell lung cancer. They tested a range of IVC doses: 1.0 g/kg, 1.2 g/kg and 1.5 g/kg (60 to 90 grams of Vitamin C for a 60 kg person). For all doses there were significant improvements in EORTC physical function scores and symptom scores.

A retrospective study was published in 2018 (Bazzan et al., 2018). This study looked at the effects of IVC on 86 patients of the Thomas Jefferson University Hospital over a 7-year period. IVC was safe, well tolerated and was effective at improving QOL for these patients.

A 2014 review cites several trials and case studies reporting positive effects by HDIVC on QOL in cancer patients with or without chemotherapy (Carr et al., 2014). There are some obvious limitations in QOL studies of HDIVC in cancer; the studies do not use a placebo control, the studies do not examine dose ranging effects, and the studies do not measure the duration of effectiveness of a dose. Essentially these limitations have not been addressed to date in research. However there is a controlled trial to run in Taiwan ("ClinicalTrials.gov Identifier: NCT03224572," 2017). This is a Parallel Assignment Randomized double-blinded controlled trial. It does not address dose ranging or duration of effect, but does address some of the general limitations of QOL trials highlighted by Carr et al. One thing to note, IVC has a short half-life. It is almost completely cleared within a few hours. The Taiwanese study is proposing to dose with IVC 30 grams once per week, only 4 doses. For most of the time during this study, the plasma levels of Vitamin C will not be elevated. It is anticipated that plasma levels are likely to be significantly elevated above normal for approximately 4-5% of the time throughout the whole study. In QOL management, Vitamin C works when it is present. For most of the time in this study the levels will be normal or maybe below normal if the patients have advanced cancer. It is really unknown at this stage how this might stack up against previous results.

Reviews

Recent reviews on the use of high dose Vitamin C in conjunction with standard medical treatments for various cancers are practical and positive. In general patients have fewer side effects, improved QOL, are better able to tolerate their medical treatments, have reduced inflammation and in some case may have prolonged life. Recent reviews also highlight some of the known or assumed mechanisms by which Vitamin C has activity as a cancer treatment, either alone or in combination with other medical therapies.

A review aimed at summary information for oncologists has been published (Klimant et al., 2018). *"The use of IV C is a safe supportive intervention to decrease inflammation in the patient and to improve symptoms related to antioxidant deficiency, disease processes, and side effects of standard cancer treatments. A proposed rationale, together with relevant clinical safety considerations for the application of IV C in oncologic supportive care, is provided."* Klimant recommends maximum doses of IVC to be capped at 25 grams. This would seem rather conservative, given that current clinical trials under ethics oversight are using doses three or four time higher than this. Klimant also recommends that IVC should be given separately to chemotherapy; this is because of any potential interaction that may occur. This is a practice that is not reflected in current clinical trials, nor is this based in evidence from clinical research. Klimant also states that Vitamin C in low dose is an antioxidant, and that in high dose it acts as a pro-oxidant. In living patients this concept is questionable, however this does appear to be the general opinion expressed in many studies today. Despite this, the Klimant review gives a good introduction to the use of IVC as an adjunct in cancer treatment and answers common criticisms or questions that oncologists have about IVC.

A common criticism applied to the clinical application of Vitamin C is that multiple approaches are taken, including a large variation in doses and protocols (Carr and Cook, 2018). In general high doses of IVC are used clinically in cancer patients, but the application of Vitamin C varies widely from patient to patient. For the treatment of individual patients this approach is not surprising, because in an integrative medicine setting individual patients have individual needs. A typical approach by integrative doctors is to titrate the dose a patient receives according to their response. While this method may be practical in a clinical setting, it is not great for clinical trials. Clinical trials require protocols, numbers, certainty, boxes. In reality when faced with a patient many doctors find that their patient sits somewhere on a spectrum and they will treat and dose accordingly. A clinical approach like this is common in medicine, not just integrative medicine. Doses of chemotherapeutic drugs are adjusted up and down all the time, new drugs are tried, and different combinations of drugs are tried depending on the response of the patient. But it is extremely difficult to apply this kind of practice to a clinical trials, it more sits in the realm of retrospective and epidemiological studies. A review of use of IVC in the USA based on 2008 statistics (Padayatty et al., 2010) found that the most common reasons for treatment were infection, cancer and fatigue. They found that doses varied widely, and the average IVC dose was 28 grams every 4 days. It was not possible to accurately determine the extent of use of IVC in 2008 in the USA from the study, but an estimate puts IVC use in this year at hundreds of

thousands of doses with 855,000 high dose vials sold. *"Doses used were as low as 1 gram or as high as 200 grams, with a similar wide range for each of the parameters queried."* The use of IVC in clinics in Australia may follow a similar pattern, i.e. integrative medicine practitioners are choosing the dose, the dose frequency and the duration of treatment based on the requirements and response of the individual patient in front of them.

There are calls for a more rigorous assessment of the use of IVC in cancer for the purpose of developing protocols. This is unlikely to happen, Vitamin C is a generic drug, there are hundreds or thousands of potential combinations of IVC dose, frequency and duration within the cohorts of cancer patients and the snowstorm of chemotherapy approaches either applied clinically or in research. It is not possible, either logistically or financially to study IVC in all of these scenarios. Information is generally taken from case reports or the published use of IVC with similar drugs.

There are however some more general approaches taken by many integrative medicine practitioners that serve as a starting point. Patients need to be medically fit to receive IVC, have normal kidney function and normal glucoe-6-phosphate dehydrogenase (G6PD) levels, and are usually started with a lower dose to assess response before the dose is escalated. Also as Carr and many others before them have pointed out patients have individual needs (Carr and Cook, 2018), the doctor may choose QOL or palliative treatment at a lower dose or proceed with a higher dose to actively try to influence the cancer.

A solidly established procedure that many integrative medicine doctors use for approaching the typical patient is the Riordan protocol. This has changed over time; in the past the protocol used 60 grams of IVC over 1 hour, or 90 grams over 90 mins. There are many published cases to reflect this practice (Riordan et al., 2004). Currently the Riordan protocol revolves around an escalating dose of IVC to reach a peak plasma concentration of 350 mg%, then tapering off the dose. The typical dose is approximately 140 grams of IVC in a week, but this varies according to the response of the patient. A QOL study from Japan (Takahashi et al., 2012) uses this technique and describes the application of the Riordan protocol in detail.

> *"A solidly established procedure that many integrative medicine doctors use for approaching the typical patient is the Riordan protocol."*

Controversy?

Is there really an issue with Vitamin C as an adjunct in cancer therapy?

There is a lack of evidence to suggest that Vitamin C interferes with chemotherapy or radiotherapy. Despite this it is still common to read or hear that Vitamin C is an antioxidant and therefore interferes with the effects of chemotherapy or radiotherapy. We must realise that these questions have largely been answered. Current clinical research is looking at very high dose IVC in combination with chemotherapy and radiotherapy. There are not just one or two trials, there are more than 30. Many of these are Phase II, some Phase III trials are planned. This means that from the point of view of ethics oversight, the ethics committees approving these trials are already satisfied that:

- Vitamin C has previously demonstrated safety
- Vitamin C has been demonstrated to be not interfering with the study drugs
- Vitamin C has previously demonstrated efficacy that needs to be investigated further.

So Does VC interfere with chemotherapy?

From extensive evidence from studies and cases so far, the short answer no, it does not. Many authors, and recently Klimant (Klimant et al., 2018) and Carr (Carr and Cook, 2018) have given extensive reviews refuting the notion that Vitamin C interferes with standard cancer therapies. On the contrary, high dose Vitamin C has emerged from research to follow the following trends:

- Standard therapies are better tolerated allowing continuation or escalation of dose
- QOL is improved; fatigue, inflammation and severity of side effects are improved
- Vitamin C levels are depleted in cancer patients and IVC adjunct therapy addresses this
- In some cases IVC and standard treatments are synergistic
- Vitamin C is not interfering with medical treatments

In vitro vs. in vivo – the disconnect

How is Vitamin C having an effect in cancer? To date there is no simple answer from this. Most research looking hard at possible mechanisms is conducted in vitro. In vitro environments have a notorious history in Vitamin C research, they come up with answers that often do not seem to apply to living patients. Clinical studies and cases are more revealing because that is where the practical on the ground information lies. There appears to be an enormous disconnect between the repeatable results of in vitro studies vs. the complex reality of response in different patients. A cancer inside a living patient does not respond the same way as the cancer cell line in a cell culture medium. This at the end of the day may be down to complex genetic or environmental factors that vary from patient to patient.

A common position taken in many studies or reviews is that at low dose Vitamin C acts as an antioxidant, but at high dose Vitamin C acts as a pro-oxidant. I.e. at a higher dose the effect of IVC therapy is to drive an oxidizing environment in or around cancer cells. The reality in living patients is likely to be much more complex than this.

In vitro Vitamin C is known to kill cancer cells in a dose/concentration dependent way (Casciari et al., 2001; Chen et al.,

2008; Frömberg et al., 2011; Klimant et al., 2018). In animals and patients high dose Vitamin C also is effective in cancer and higher dose/concentration is sometimes more effective. Protocols are used that get very high plasma concentration based on the positive and reproducible cell killing results from in vitro studies (Padayatty, 2006; Peng et al., 2009; Riordan et al., 2003).

There are many theories about why this works. One very popular theory is the pro-oxidant theory:

- Extracellular fluid (ECF) contains proteins which contain redox active metals like Cu or Fe.
- Vitamin C in the ECF reduces these protein bound metals (3+ → 2+).
- The metals then react with molecular oxygen to form superoxide (O_2.-).
- 2 superoxide molecules react to form hydrogen peroxide (H_20_2). This is called dismutation and might require enzymes like superoxide dismutase (SOD).

The pro-oxidant theory says that the presence of Vitamin C (a reducing molecule) forms H_20_2. H_20_2 is an oxidising molecule. H_20_2 causes cancer cell damage/death. This has been demonstrated in vitro many times (Chen et al., 2005; Deubzer et al., 2010; Zheng et al., 2002) and is cited as the standard theory about how Vitamin C works in most contemporary reviews and studies.

The pro-oxidant theory shows that the amount of H_20_2 produced increases with the amount of Vitamin C present. This all happens in the ECF. The H_20_2 produced diffuses over the cancer cell membrane and affects the cancer cell directly. It may turn on cell death mechanisms (Chen et al., 2007). This pro-oxidant effect may work with any high dose reducing agent. In cancer treatment Vitamin C is used because it is safe in very high doses and can get very high concentrations in the ECF in a patient. The Vitamin C must be in its reduced form, i.e. ascorbate. Otherwise it does not work.

The vitamin C as ascorbate is a reducing agent. This means it is an electron donor (it gives an electron). This is all it does. This is how antioxidants work. For Vitamin C to give an electron to form H_20_2 these must be in the ECF:

- Molecular O_2
- A redox active protein with Cu or Fe metal ions that can react with Vitamin C and O_2

ECF will contain various proteins which contain redox active metals. But ECF may not contain a lot of molecular O_2. $O_2$is usually bound in transporters. In vitro there is always O_2 present in the medium because the medium is exposed to air. The medium may also be exposed to light and some redox active proteins are activated by light (Lavoie, 2004; Silvers et al., 2001).

Another problem with using medium in in vitro experiments is that the medium is different to ECF. The results might not be the same as in living systems. Experiments in medium can produce in vitro artefacts (Carr and Frei, 1999; Suh et al., 2003). When experiments to test the pro-oxidant theory have been tried in animals the ECF has been extracted to test for H_20_2 (Chen et al., 2007).

DO ANTI-OXIDANTS HAVE AN ESSENTIALLY PRO-OXIDANT EFFECT IN VIVO?

As originally reported by Dettman (Dettman and Meakin, 2017) many studies demonstrate the pro-oxidant effect of Vitamin C and various other antioxidants in vitro. Only one study has looked at this for Vitamin C in vivo, with the authors reporting that: “The data shows that pharmacologic ascorbate is a prodrug for preferential steady-state formation of ascorbyl free radical - Asc(*-) and H_20_2 in the extracellular space but not blood” (Chen et al., 2007). The probes to collect extracellular fluid eluate were flushed with saline for 30 minutes and samples were collected over 30 minutes.

There are two essential problems here (Dettman and Meakin, 2017):

- Firstly, before collection of extracellular fluid, considerable change has been made to the microenvironment through flushing of the inserted microprobe for 30 minutes with normal saline, prior to obtaining a sample of the extracellular fluid. The basis for this collection technique is a method published by Tossman et al. in 1986 for the collection of amino acids, not the very labile Vitamin C (Tossman and Ungerstedt, 1986).
- Secondly, ECF (extracellular fluid) and blood have to be collected and analysed, collection by definition is ex-vivo and exposes the collected fluid to an environment that is different to in vivo conditions. This by its nature changes the redox environment of Vitamin C and the large risk is that products formed may not be the same ones or at the same concentration as seen in situ in the animal. In vitro and ex vivo Vitamin C research has a long history of drawing conclusions gleaned from experimental artefacts.

So, does Vitamin C act as a pro-oxidant in vivo? Really this has not been extensively tested however research from 1999 (Carr and Frei, 1999) testing the effect of trace elements to induce an increase in oxidative biomarkers in the presence of Vitamin C concludes that it does not – however this was only testing an increase in biomarkers in the bloodstream, they did not measure hydrogen peroxide nor measure any oxidative effects in the extracellular fluid of cancer cells.

The action of ascorbate as a pro-drug to generate hydrogen peroxide is abolished in in vitro systems when catalase is added (Chen et al., 2005). Catalase breaks down hydrogen peroxide into water and oxygen. In living animals catalase is produced in multiple compartments, such as in red blood cells and serves to limit hydrogen peroxide levels. Theories about why Vitamin C acts as a pro-drug to produce hydrogen peroxide include ideas that catalase levels are low in cancer cells and the extracellular fluid, leading to the buildup of levels of hydrogen peroxide inside cancer cells to the point where it has a detrimental effect. This idea has come about because in vitro Vitamin C causes cell killing in cancer cells but not normal cells (Chen et al., 2005). The catalase concentration varies in different cancer cell lines, but a low level is a common finding (Rouleau et al., 2016): *“Hep G2 cells (an immortal liver cell line used in studies) and other cancer cells exhibited markedly lower levels of catalase and glutathione peroxidase than hepatocytes isolated from normal liver tissue and inhibition of catalase and glutathione reductase sensitized primary hepatocytes to ascorbate cytotoxicity and increased cytotoxicity of pharmacologic ascorbate in cancer cells”. However Rouleau*

et al. also found that "Treatment of different cancer cell types with glucose oxidase as an H_2O_2 generating system was less cytotoxic than treatment with pharmacologic ascorbate at comparable rates of H_2O_2 generation, ***indicating that pharmacologic ascorbate had other actions in addition to generation of extracellular peroxide****."*

But true or not, the pro-oxidant theory really is the current pet theory though as to how Vitamin C works. All that Vitamin C does is to give an electron. In this way it is always an antioxidant. Chen (Chen et al., 2005) and others (Carr and Cook, 2018) prefer to refer to Vitamin C as a "pro drug" rather than a pro-oxidant, the term is more descriptive of how Vitamin C may participate in in vitro systems. But whatever you call this *it has not yet been proved that the pro-oxidant theory is true because it has not yet been proved in living animals*.

Many articles appear about the "redox" effects of Vitamin C – such that ascorbate is a reducing agent (electron donor) and dehydroascorbate is an oxidizing agent (electron receiver). It may be concluded that potentially the major function of Vitamin C depends on the redox state of the tissue, however dehydroascorbate is relatively unstable with a quite short half-life and is rapidly broken down unless converted back to the more stable ascorbyl free radical or ascorbate. In the blood stream Vitamin C almost totally exists as the ascorbate anion (Rumsey and Levine, 1998) so the major function of ascorbate is therefore as a reducing agent.

The goal of reaching high plasma concentrations with IVC of 360 mg% comes from in vitro research based on repeatable cancer cell death in cell culture (Casciari et al., 2001; Chen et al., 2005). High dose intravenous Vitamin C in patients almost never has the same spectacular effects on cancer cells seen in test tube experiments. But Vitamin C is effective in cancer patients. Is the Vitamin C doing something else in living patients? The answer to this is probably yes, there are multiple ways that Vitamin C may be involved, most of which have little or nothing to do with hydrogen peroxide.

Mechanisms of Vitamin C action in cancer

There is an enormous amount of research on other mechanisms of Vitamin C action in cancer, most of which have little to do with a pro-oxidant effect or hydrogen peroxide. Contemporary research is heavily focused on gene modification, epigenetics and the chains of effects that this can have on tumour promotion or control. It is likely that a combination of effects is occurring in patients, that multiple activities take place concurrently such as epigenetic modification, protection of cell death genes, pro-drug effects and control of inflammation and immune response.

Here is a brief but not exhaustive categorisation of research into Vitamin C activity in cancer. For each of these there is a considerable amount of research:

- Pro-oxidant (pro-drug) effects (H_2O_2).
- Protection of cell death genes (Not H_2O_2).
- Decreased HIF-alpha activity (Not H_2O_2).
- Glucose starvation by blockade of GLUT receptors (Not H_2O_2).
- Control of iron chemistry.
- Control of deoxyribonuclease (DNase helps control cell division and cancer cell growth).
- Genetic effects (hydroxylation of methylated cytosine, TET enzymes, BRAF, KRAS, Not H_2O_2?).
- Control of cell death genes – caspases and cell cycle control (H_2O_2?).
- Control of intracellular pH and altered Ca++ chemistry (Not H_2O_2).
- Inhibition of Angiogenesis.
- Integrity of ECM and inhibition of migration and metastasis (increased collagen and proteoglycan and decreased hyaluronidase).
- Immune effects: + NK cells, + lymphoblastosis, + phagocytosis, + chemotaxis – normalisation of immune response (sepsis etc.) (Not H_2O_2).
- Chelating effects (Not H_2O_2).
- General antioxidant effects (Not H_2O_2, anti-inflammatory.)

Let's expand briefly on some of these:

Protection of cell death genes

There are numerous studies published that demonstrate that vitamin C can protect cancer cells from chromosome damage. In combination with certain chemotherapeutic drugs, vitamin C is anti-clastogenic (clastogenic means produces chromosome breaks) if in sufficient concentration (Nefic, 2001). Vitamin C in combination with cisplatin will reduce the chromosome damage that cisplatin would otherwise cause. It is assumed that the extent of chromosome damage produced by a drug is directly related to that drug's effectiveness - as a result there are many people who conclude that vitamin C interacts negatively with chemotherapy. It is clear from many clinical trials and observations however that vitamin C in general *improves* the effectiveness of these drugs and also decreases the side effects on normal tissue. Chromosome damage in itself is not a reliable predictor of the fate of the cell because chromosome damage in itself does not necessarily cause cell death. Cell death is largely mediated by the expression of genes that code for proteins that initiate programmed cell death events. Despite the anticlastogenic nature of vitamin C, vitamin C (if in sufficient concentration) has the effect of increasing the expression of these genes in cancer cells (Catani et al., 2002; Reddy et al., 2001). In fact it is reasonable to assume that gross damage to DNA might result in damage to the programmed cell death genes themselves, rendering the cell resistant to chemotherapy drugs (Bakhoum et al., 2018; Schmitt and Lowe, 1999). Chromosome damage is also related to metastasis (Bakhoum et al., 2018).

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Decreased HIF-alpha activity

Accumulation of hypoxia inducible factor-1 alpha (HIF-1α) in malignant tissue is known to contribute to oncogenic progression and is inversely associated with patient survival (Fischer and Miles, 2017). Expression of HIF-1α regulates antiapoptotic proteins of the Bcl-2 (B-cell lymphoma 2) gene family, such as Mcl-1, Bcl-xL, and Bcl-2. High expression of HIF-1α leads to high levels of antiapoptotic Bcl-2 proteins and failure of apoptosis in cancer cells (Kawada et al., 2013). Also damage to Bcl-2 genes is strongly associated with cancer progression and drug resistance.

Here's how it's thought to work:

- ↑ NF-κB (a pro-inflammatory cytokine) is associated with inflammation and further cytokine production – progression of cancer
- ↑ NF-κB ++ expression of HIF-1α and antiapoptotic Bcl-2 - failure of apoptosis
- High cellular Vitamin C inhibits the nuclear translocation of NF-κB
- ↑ VIT C ↓ production of HIF-alpha

Lowering NF-κB with Vitamin C lowers HIF-1α and thus antiapoptotic Bcl-2 levels. Apoptosis is restored and cancer cells respond (Kawada et al., 2013).

Also Vitamin C aids HIF-1α breakdown (Kawada et al., 2013):

- Vitamin C is a cofactor for various HIF hydroxylases and inhibitors
  - PHD 1-3 (various prolyl hydroxylases)
  - FIH (factor inhibiting HIF)
  - HIF-1α is degraded by PHD and FIH

Lowering of HIF-1α by Vitamin C is a significant and growing area of research. The effect does not require very high plasma concentrations of Vitamin C and may be a significant part of the response to Vitamin C in patients.

Glucose starvation by blockade of GLUT receptors

Cancer cells have been reported to depend heavily on glycolysis (anaerobic metabolism) for their energy, leading to a heavy consumption of glucose. This is called the Warburg effect (Aguilera et al., 2016). Glycolysis is inefficient and consequently if glucose entry to the cell can be blocked, the cell can be "starved" leading to severe stress and cell death.

Oxidised Vitamin C (dehydroascorbate – DHAA) is a direct competitor with glucose for uptake by GLUT transporters. If DHAA is abundant extracellularly, glucose uptake into the cancer cell will be lowered. In advanced cancer there will almost certainly lowered antioxidant levels and significant amounts of DHAA available in the ECF due to the associated inflammatory environment around cells found in cancer patients. If starved of glucose Cancer cells that rely on glycolysis for energy become acidic, and become very sensitive to oxidative stress – the pro-oxidant theory of cancer cell killing (Deubzer et al., 2010). It is proposed that in many cancer cells a combination of extracellular H_2O_2 production by reduced Vitamin C (ascorbate) and glucose competition by oxidised Vitamin C (DHAA) is lethal.

> *"Vitamin C has a direct effect on DNA methyltransferases."*

Genetic effects

Vitamin C is involved in demethylation of DNA and histones. Vitamin C has a direct effect on DNA methyltransferases. SNPs (single nucleotide polymorphisms) in Vitamin C transporters or variations in transporter expression are related to various cancers. Deficiency = phenotypic alterations with effects in:

- Embryonic and postnatal development
- Aging
- Cancer
- Various diseases

Histones

Histones are a family of 13 alkaline proteins found in eukaryotic cell nuclei. Histones package and order the DNA into nucleosomes. Each has different functions:

- Central role in gene regulation.
- Central role in DNA repair
- Methylation state of various histones related to transcription and/or repression of genes. (mono, di or tri methylation)
- Most commonly methylation = activation

Vitamin C is critical for specific histone demethylases that catalyze histone demethylation. Vitamin C is a cofactor for JmjC domain-containing histone demethylases (JmjC = Jumonji C):

- Critical for maintaining epigenetic regulation
- Vit C maintains Fe 2+

5-methylcytosine (5-mC)

Methylation at the C5 position of cytosine (5-methylcytosine, 5mC) is the major covalent modification of mammalian DNA. 5-mC plays essential roles in regulating transcription and maintaining genome stability and cellular identity (Camarena and Wang, 2016; Gustafson et al., 2015).

Methylcytosine Dioxygenases TET

TETs are responsible for part of DNA demethylation. Vitamin C is a cofactor in TET (TET = methylcytosine dioxygenase ten-eleven translocation)

- TET depends on Fe2+
- Vit C maintains Fe 2+
- TET - catalyze the hydroxylation of 5mC to 5-hydroxymethylcytosine (5hmC), allows DNA demethylation
- Control of TET enzymes with Vitamin C – big and expanding area of current research

"The availability of ascorbate to TETs and some JmjC domain-containing histone demethylases in the nucleus is now considered critical in maintaining the epigenome." (Camarena and Wang, 2016)

TET-mediated DNA active demethylation appears to be downregulated in most, if not all, types of human cancer. A low level, or even loss, of 5hmC has been recognized as a novel epigenetic hallmark of cancer. *"It has been shown that*

the overexpression of TET1 in breast cancer and the overexpression TET2 in melanoma could partially reestablish a normal 5hmC profile in these cancer cells and decrease malignancy, especially invasiveness."
(Camarena and Wang, 2016)

Several studies to date have examined the effects of Vitamin C on TET levels and expression in various cancers (Cimmino et al., 2017; Hore, 2017; Miller and Ebert, 2017; Shenoy et al., 2017) and many more. This is a current and strongly trending area of research and can be found in current reviews (Carr and Cook, 2018).

DNA Methyltransferases

The transfer of a methyl group from the donor S-adenosylmethionine to a cytosine is catalyzed by DNA methyltransferases (DNMTs) (Young et al., 2015). The overexpression OF DNMTs and/or the inability to demethylate 5-methylcytosine are common hallmarks of cancer. As a general rule, too much DNA methylation related to cancer and progression of cancer (note that this is not always the case). In an in vitro study Vitamin C in pharmacological doses (8mM) inhibited DNMT activity in human melanoma cells (Venturelli et al., 2014). Venturelli further goes on to summarise the thinking around Vitamin C in 2015: *"In recent years it became evident that high-dose ascorbate in the millimolar range bears selective cytotoxic effects on cancer cells in vitro and in vivo. This anticancer effect is dose dependent, catalyzed by serum components and mediated by reactive oxygen species and ascorbyl radicals, making ascorbate a pro-oxidative pro-drug that catalyzes hydrogen peroxide production in tissues instead of acting as a radical scavenger. It further depends on HIF-1 signaling and oxygen pressure, and shows a strong epigenetic signature (alteration of DNA-methylation and induction of tumor-suppressing microRNAs in cancer cells)."* (Venturelli et al., 2015)

From a current perspective, Vitamin C appears to be having the following genetic/epigenetic effects. These are generalisations; of course this does not apply in all situations:

- Overmethylation or inability to demethylate Histones related to cancer
- Overmethylation or inability to demethylate DNA related to cancer
- Vit C ↓ histone methylation – regulation
- Vit C ↑ TET expression and DNA demethylation – regulation
- Vit C ↓ DNMT activity and DNA methylation – regulation
- Vit C deficiency – this all goes wrong!
- Replace Vit C – normalises these processes, slows progression, ↓ inflammation and promotion

General antioxidant and immune effects

Patients with advanced cancer are maximally stressed with toxic interventions and may have significant systemic inflammation. This leads to significant depletion in antioxidant capacity – Vitamin C, glutathione (GSH) etc. Inflammation is strongly related to cancer progression.

Vitamin C as an adjunct therapy in cancer treatment improves quality of life (QOL). It is likely that the effects are largely due to the replenishment of antioxidant levels in otherwise highly antioxidant depleted individuals. Vitamin C has significant and direct impacts in this setting on inflammation, controlling the progression of inflammation, reducing the side effects of standard therapies and improving fatigue. These effects are probably related to immune control, regulation of cytokine response, prevention of progression of immune response and normalization of immune response.

The effects of Vitamin C on immune function and response are no longer doubted, however the extent of the effect at different dose levels in different situations is still open to question. Vitamin C has recently been tested in the control of sepsis/septic shock (Marik, 2018) and is currently at the centre of multi centre clinical trials into the management of septic shock ("Vitamin C Sepsis - ClinicalTrials.gov," 2019). Intravenous Vitamin C in very high doses has also been used in burns units to control fluid resuscitation requirements and aid in the management of severe burns (Kahn et al., 2011). It is not surprising then that Vitamin C treatment in cancer patients has effects on controlling inflammation and normalizing immune responses.

Carr et al. have recently undertaken an extensive review of the role of Vitamin C in immune response (Carr and Maggini, 2017). They document numerous functions of Vitamin C and conclude that: *"Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. In turn, infections significantly impact on vitamin C levels due to enhanced inflammation and metabolic requirements. Furthermore, supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections."*

Vitamin C has many effects on the immune system. Some of these are observational, but many have documented mechanisms:

- Stimulating or driving the immune system so normal function may have dramatic effects in cancer:
  - Recognition and destruction of cancer
  - Direct stimulation of depleted immunity
  - Control of overstimulated immunity, control of cytokines etc.
  - Effects on viruses, cancer viruses and concomitant infections
  - Metabolic effects – synergism with antibiotics, e.g. doxycycline and Vitamin C

Vitamin C directly scavenges radicals produced by inflammatory pathways, *if it is in sufficient concentration.*

Vit C has a significant anti-histamine effect and increases chemotaxis. In a clinical trial 10 subjects ingested a placebo during weeks 1, 2, 5 and 6, and 2 g/day of VC during weeks 3 and 4 (Johnston et al., 1992): *"…Neutrophil chemotaxis rose 19% (NS) during VC administration, and fell 30% after VC withdrawal, but these changes were not correlated to plasma ascorbate levels…" and "…Chemotaxis was inversely correlated to blood histamine and, compared to baseline and withdrawal values, histamine levels were depressed 38% following VC supplementation."*

Analysis of 437 human blood samples has shown that when the plasma ascorbate level falls below 1 mg%, the whole blood histamine level increases exponentially as the ascorbic acid level decreases (Clemetson, 1980). In a further review Clemetson has documented the histamine lowering effects of Vitamin C (Clemetson, 2004).

Directly related to cancer patients, Mikirova et al sowed that Vitamin C administration controls inflammation by demonstrating significant reductions in inflammatory markers (Mikirova et al., 2012): *"…high dose intravenous ascorbic acid therapy affects C-reactive protein levels and pro-inflammation cytokines in cancer patients. In our study, we found that modulation of inflammation by IVC correlated with decreases in tumor marker levels."*

Where are we?

The above summaries represent current areas of research. By no means does this imply that other documented mechanisms by which Vitamin C may act have been abandoned. Research money and directions are fickle, the research questions follow trends and they come and go. It is not uncommon for a research question from long ago to be taken up again. Currently we have significant research being done in epigenetics, HIF alpha, inflammation and immune response in cancer. Multiple drugs with Vitamin C and now radiotherapy with Vitamin C are prominent in research. That does not make older research directions wrong, they may just be sleeping.

Clearly the interactions between Vitamin C and standard therapies in cancer patients produce strongly individual responses. The current conservative thinking is moving towards genotyping of patients and cancers and targeting appropriate therapies. This also applies to Vitamin C and its known interactions with the epigenome. Cancer is however a chameleon, it shifts, changes shape, produces genetically different daughters and defies being put in a box. For these reasons many integrative medicine doctors choose to use Vitamin C in a less targeted way; they seek to improve the immune response, control and limit inflammation and overall try to improve the quality of life of the patient. It may mean a different approach for every patient depending on the cancer, the stage of the disease, the previous treatments and the response of the individual.

Vitamin C as an adjunct treatment does not appear to interfere with standard therapies. In an unwritten agreement, most integrative medicine doctors choose to administer Vitamin C away from chemotherapy; prior to chemotherapy or after the drug has been cleared. This is a general recommendation of Klimant (Klimant et al., 2018) and others. This is not however a practice that is represented in current research, especially in the setting of radiotherapy.

There is enough documentation around the safety and efficacy of Vitamin C as an adjunct treatment alongside standard therapies that it should no longer be considered controversial. Current research reflects this position; with studies getting larger and high dose Vitamin C being used with multiple drugs, radiation, and multiple protocols, all approved by ethics oversight. Are we in a position where we know what the best protocol is for any given patient? No. But a reasonable response is to collect cases and move towards the analysis of what is working and what is not.

The goal of integrative medicine is the same as standard medicine; a good outcome for the patient. That might be palliation, improved QOL, regression, remission or control. For the cancer patient research tells us that Vitamin C has a lot to offer. Is it going to work for everyone? No. But nothing does. Is it toxic? No. Does it interfere with standard treatments? No. Vitamin C as an adjunct in the treatment of cancer patients is a reasonable approach for integrative medicine doctors and also in oncology.

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Version ID: AIMN_Review_Chemotherapy_and_Vitamin_C_May_2019