Commentary

The controversial place of vitamin C in cancer treatment

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ABSTRACT

In 2008, we celebrate the 50th anniversary of the discovery of vitamin C. Since then, we know that vitamin C possesses few pharmacological actions although it is still perceived by the public as a "miracle-pill" capable to heal a variety of illnesses. Cancer is one of the most common diseases for which a beneficial role of vitamin C has been claimed. Thus, its dietary use has been proposed in cancer prevention for several years. Apart from this nutritional aspect, an extensive and often confusing literature exists about the use of vitamin C in cancer that has considerably discredited its use. Nevertheless, recent pharmacokinetic data suggest that pharmacologic concentrations of vitamin C can be achieved by intravenous injections. Since these concentrations exhibit anticancer activities in vitro, this raises the controversial question of the re-evaluation of vitamin C in cancer treatment. Therefore, the purpose of this commentary is to make a critical review of our current knowledge of vitamin C, focusing on the rationale that could support its use in cancer therapy.

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1. Introduction

1.1. A few words about vitamin C history

Vitamin C (ascorbic acid) is intimately linked to scurvy, a deficiency disease known since the time of the Crusades and which occurs in humans whose diet is deficient in fresh fruits and vegetables. Scurvy symptoms are associated with a defect in collagen synthesis and include failure of wounds to heal, defects in tooth formation and rupture of the capillaries leading to petechia and ecchymoses. In the mid-18th century James Lind demonstrated that the juice of fresh citrus fruits cures scurvy. The active agent was a new glucose derivative (the enolic form of 3-oxo-1-gulofuranolactone) that was isolated and first coined "hexuronic acid" by the Hungarian physician Szent-Györgyi [1]. Few years later, Szent-Györgyi described the antiscorbutic activity of this compound and gave it the trivial name of ascorbic acid (AA) to designate its function in preventing scurvy [2,3]. The chemical structure of ascorbic acid was soon established in several laboratories (Fig. 1), definitely recognized as vitamin C and widely produced.

1.2. Synthesis and metabolism

Actually, ascorbic acid can be generated de novo by many species. This production occurs in the hexuronic acid pathway of the liver or the kidney, due to the activity of a particular enzyme: the gulonolactone oxidase. Since humans (as well as other primates, guinea pigs and a few bat species) lack this enzyme, they cannot synthesize ascorbic acid and, therefore, they must find their high requirements in foods, notably in fruits and vegetables [4]. That is the reason why ascorbic acid is a vitamin for humans.

Ascorbic acid is readily absorbed from the intestine and the absorption of dietary ascorbate is nearly complete. However, it
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1.3. Redox properties

Vitamin C is a potent water-soluble antioxidant whose activity can be explained by two facts [15]. First, both ascorbic acid and ascorbyl radical, its one-electron oxidized state (Fig. 1), present low one-electron reduction potentials, 282 and -174 mV, respectively [16]. Therefore, they can reduce most biologically relevant radicals and oxidants such as hydroxyl radical, superoxide anion, hypochlorous acid or singlet oxygen. Second, ascorbate can be easily regenerated. Indeed, the ascorbyl radical (\(A^+\)), which is relatively stable due to resonance stabilization, may disproportionate to ascorbic acid and dehydroascorbate (reaction (1)) [15]:

\[
2A^- + 2H^+ \rightarrow AA + DHA
\]

Furthermore, ascorbate can be regenerated from both DHA and the ascorbyl radical either enzymatically (e.g. thioredoxin reductase, glutaredoxin) or non-enzymatically (e.g. glutathione, lidic acid) [15-15,17]. Additionally, vitamin C may cooperate with vitamin E (\(\alpha\)-tocopherol) since ascorbate can transfer hydrogen to \(\alpha\)-tocopheroxy radicals, thus regenerating vitamin E. Such an antioxidant recycling allows the transfer of oxidizing equivalents from the hydrophobic phases into the aqueous phases, e.g. from the membrane to the cytosol. This recycling could be of high importance for cells since their membranes, which are hydrophobic and sensitive to oxidation, would be cleared of radicals. Nevertheless, this mechanism was demonstrated in vitro and its occurrence in vivo is still uncertain [15].

Strikingly, ascorbate may also lead to pro-oxidant effects, especially through the reduction of transition metal ions such as iron and copper. Upon their reduction by ascorbate (reaction (2)), these metal ions can react with hydrogen peroxide (reaction (3)), known as Fenton reaction) or lipid hydroperoxides (reaction (4)) to produce either hydroxyl radicals or lipid alkoxyl radicals [18-20]:

\[
\begin{align*}
\text{AH}^- + \text{Fe}^{3+}/\text{Cu}^{2+} &\rightarrow A^{+} + \text{Fe}^{2+}/\text{Cu}^{+} + \text{H}^+ \\
\text{H}_2\text{O}_2 + \text{Fe}^{3+}/\text{Cu}^{2+} &\rightarrow \text{HO}^+ + \text{Fe}^{2+}/\text{Cu}^{3+} + \text{HO}^- \\
\text{LOOH} + \text{Fe}^{3+}/\text{Cu}^{2+} &\rightarrow \text{LO}^+ + \text{Fe}^{2+}/\text{Cu}^{3+} + \text{HO}^-
\end{align*}
\]

These reactions between ascorbate and transition metals are thought to be responsible for the pro-oxidant and cytotoxic properties of ascorbate observed in vitro [21]. Ascorbate is also known to induce the release of iron bound to ferritin or haemosiderin, which could take part in the lipid peroxidation process driven by the Fenton reaction [22]. Transition metals are not the only compounds that react with ascorbate. Indeed, quinoid compounds can be reduced by ascorbate (reaction (5)), leading to the generation of a semiquinone radical that is readily reoxidized by molecular oxygen (reaction (6)):
there is an enhancement of the damage induced by quinoid compounds [23,24].

1.4. Known biological activities

Apart from its redox properties, vitamin C possesses a variety of biological functions. It contributes to catalysis by donating electrons to metal ion cofactors of hydroxylase enzymes. Thus, vitamin C is required for or facilitates the conversion of certain proline and lysine residues to hydroxyproline and hydroxylysine in the course of collagen synthesis and other post-translational processes, such as the oxidation of lysine side chains in proteins to provide hydroxylmethyllysine for carnosine synthesis, the conversion of folate to folinic acid and conversion of dopamine to norepinephrine [25]. Besides its role as cofactor in hydroxylation reactions, ascorbic acid is also involved in iron absorption. Indeed, it overcomes the inhibitory effect of strong metal chelators (e.g. phytic acid) that reduce the iron bioavailability. This explains why ascorbic acid is considered as a potent enhancer of iron absorption [26].

In spite of its importance for human metabolism, vitamin C possesses few pharmacological actions, with the exception of the scurvy-inducing individual. Nevertheless, an extensive literature exists on the application of this vitamin to a wide variety of diseases. Thus, for many people, vitamin C is believed to prevent or cure viral respiratory infections and to be beneficial in both cardiovascular diseases and cancer. Although there is no clinical evidence as yet that vitamin C can be beneficial in any one of these indications [27,28], it is still perceived by the public as a miracle-pill.

2. Molecular considerations

2.1. Induction of oxidative stress

Many papers have described that millimolar concentrations of ascorbate have a deep inhibitory effect on the growth of several cancer cell lines in vitro [29-33]. Actually, it seems that such cytotoxic activity of vitamin C relies on its ability to generate reactive oxygen species rather than its popular antioxidant action. This is paradoxical but, as previously described (Section 1.3), ascorbic acid may have pro-oxidant and even mutagenic effects in the presence of transition metals [18,34,35]. In vitro, the cytotoxicity of ascorbate is intimately linked to the generation of hydrogen peroxide. However, the mechanism underlying the production of this latter species is unclear and we still do not know whether specific transition metals (iron and copper, notably) or proteins are required for ascorbate toxicity [33]. It should be noted that in vitro data concerning the production of hydrogen peroxide by ascorbate are sometimes difficult to interpret since they can be influenced by cell culture conditions (i.e. medium and serum components) [21,36].

Whatever the precise mechanisms underlying the production of hydrogen peroxide by vitamin C in vitro, another important question is whether vitamin C can induce the in vivo formation of ROS. Supporting this hypothesis, Chen et al. have reported a concentration of approximately 20 μM of hydrogen peroxide in extracellular fluids following the intravenous administration of 0.5 g/kg of vitamin C in rats [37]. The same authors have obtained similar data in mice bearing human tumor xenografts [38]. The mechanisms leading to hydrogen peroxide production in vivo are unknown but likely involve protein-bound metal cations. Interestingly, the in vivo generation of hydrogen peroxide by ascorbate seems possible in extracellular fluids and not in blood because red blood cells exhibit catalase and glutathione peroxidase activities which efficiently remove any trace of hydrogen peroxide [33]. The site of hydrogen peroxide production is thus a critical parameter for the activity of ascorbate, leading to the concept that vitamin C could act as a prodrug to deliver hydrogen peroxide into tissues [33,37]. Supporting the in vivo formation of ROS, several papers have described the occurrence of oxidative damage upon vitamin C exposure [39-41] although the relevance of some of these observations is still actively debated [15].

Interestingly, the oxidative stress promoted by ascorbate seems to preferentially target cancer cells which exhibit a greater sensitivity towards ascorbate comparing to their normal counterparts [33,42,43]. The origin of this difference of sensitivity between normal and cancer cells is unknown but different hypotheses can be formulated. Thus, it has been shown that cancer cells readily take up ascorbate. Indeed, most tumors overexpress facilitative glucose transporters because of their high glycolytic metabolism which requires high glucose supply [44]. As a consequence, dehydroascorbic acid can be transported by GLUTs, leading to the accumulation of vitamin C in tumors [45]. This mechanism has been observed in several models [9,45-47] and could partly explain the greater sensitivity of cancer cells towards ascorbic acid. In addition to the greater vitamin C uptake by cancer cells, these latter have been described to be more sensitive towards oxidative stress. Indeed, oncogenic transformation (e.g. by c-Myc or Bcr-Abi) has been reported to induce a higher basal status of intracellular ROS [48-50] associated with a greater sensitivity towards oxidative stress [51,52]. The rationale is that cancer cells, which present high endogenous levels of ROS, would be preferentially killed by any ROS-promoting agent [53]. Furthermore, a low antioxidant status due to an imbalance in antioxidant enzyme levels has been described in various cancer cell lines that could also participate in their sensitivity to ROS [54-56]. Several studies have thus reported decreased levels of copper- and zinc-containing superoxide dismutase (CuZnSOD) as well as of catalase and glutathione peroxidase in tumors [55,57-61]. Although these data support an alteration in the expression of antioxidants enzymes, it remains hazardous to make a global conclusion about the antioxidant status presented by cancer cells, and that for a variety of reasons: few studies are available, absence of comparison with healthy tissues, artefacts due to cell culture conditions, etc. [62].

2.2. Influence on anticancer treatments

A critical aspect before considering the use of redox modulating agents in cancer patients is the putative influence of these agents on the activity of radio- and chemotherapy. Indeed, it is well known that at least a part of the efficacy of classical anticancer treatments relies on the generation of an
oxidative stress. For instance, radiotherapy generates reactive oxygen species (i.e. free hydroxyl radicals) in irradiated tissues by the ionization of cellular water [63]. The situation is less clear with chemotherapies given that they act through specific ways. However, evidence suggest that oxidative stress may be involved in the toxicity of some drugs, such as paclitaxel [64,65]. Therefore, the concomitant use of anti-oxidants and chemotherapies must be carefully envisaged [66], preferentially after preclinical studies.

As illustrated in Table 1, vitamin C has been reported to increase the efficacy of several chemotherapeutic drugs either in vitro or in vivo [30,67–75], and similar data have been obtained with radiotherapy [30,76]. Nevertheless, it should be noted that the activity of some agents seems to decrease when ascorbic acid is used simultaneously. Actually, this can be the consequence of a direct inactivation of the drug in vitro by vitamin C, as nicely described in the case of bortezomib [77]. It is however uncertain that such reactions occur in vivo. Alternatively, it has been observed that cells exposed to dehydroascorbic acid (which allows intracellular loading of ascorbate) might be slightly protected against arsenic trioxide or TRAIL ligand [78,79], but again, these data require further confirmation in vivo. Importantly, it should be remarked that the oral supplementation of vitamin C (together with other antioxidants) seems to have no influence on the outcome of patients undergoing chemotherapy regimens, suggesting that it did not protect cancer cells from oxidative damage induced by chemotherapy [80]. Taken together, these data suggest that ascorbic acid promotes the activity of several anticancer treatments although its inclusion should be carefully envisaged on the basis of preclinical results.

2.3. Influence on tumor metabolism

Solid human tumors contain regions of very low oxygen concentrations, a phenomenon called hypoxia. Actually, the uncontrolled proliferation of cancer cells leads to the colonization of areas which are at increasing distance from blood vessels. Given the poor limit of oxygen diffusion (100 μm) these areas become rapidly hypoxic [81]. Hypoxia is further enhanced by the increasing metabolic demands of cancer cells, as well as by the tortuous vasculature presented by tumors which results in a highly unstable blood flow. In order to survive, cancer cells must therefore adapt themselves to hypoxia, and this process is mainly achieved by the activation of the transcription factor hypoxia-inducible factor 1 or HIF-1 [82]. HIF-1α is a heterodimer consisting of a constitutively expressed HIF-1α subunit and a regulated HIF-1α subunit whose the expression is tightly controlled by oxygen levels. Basically, in the presence of oxygen (normoxia) O2-dependent hydroxylation of proline residues in HIF-1α by prolyl hydroxylases is required for the binding of the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex that targets HIF-1α for degradation by the 26S proteasome. Prolyl hydroxylases belong to a subfamily of dioxygenases that uses oxygen and 2-oxoglutarate as co-substrates. They also contain a non-heme iron group that is critical for their activity [83]. Under hypoxic conditions, the activity of HIF-1 hydroxylases decreases, resulting in a decreased rate of HIF-1α degradation and the transcriptional activation of HIF-1 target genes which are known to encode angiogenic factors, glycolytic enzymes, survival factors and invasion factors.

Since the activity of HIF-1 is mandatory for solid tumor progression, its inhibition represents a very attractive target for cancer therapy [84,85]. Interestingly, the in vitro activity of prolyl hydroxylases is enhanced in the presence of ascorbate, and loading cells with ascorbate results in the inhibition of HIF-1 activation by hypoxia [86,87]. Actually, ascorbate plays the role of cofactor for prolyl hydroxylases since it maintains the iron centre of hydroxylases in a reduced state, thus optimising their activity. Supporting an inhibitory effect of ascorbate on HIF-1 activity, similar data have been obtained in vivo, by using a MYC-mediated tumorigenesis model [88]. Given the critical role played by HIF-1 in tumor growth as well as its influence on the response to anticancer therapies [89], its inhibition by ascorbate represents an additional mechanism supporting the anticancer properties of this compound.

### Table 1: Influence of vitamin C on the efficacy of different chemotherapeutic drugs.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Influence of vitamin C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>a</td>
<td>[30]</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>b</td>
<td>[72]</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>a</td>
<td>[30]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>a</td>
<td>[70]</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>a</td>
<td>[70]</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>b</td>
<td>[72]</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>b</td>
<td>[72]</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>b</td>
<td>[72]</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>b</td>
<td>[72]</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>b</td>
<td>[72]</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>b</td>
<td>[73]</td>
</tr>
<tr>
<td>Vincristine</td>
<td>b</td>
<td>[67]</td>
</tr>
<tr>
<td>X-rays</td>
<td>a</td>
<td>[30]</td>
</tr>
<tr>
<td>tirosinex</td>
<td>a</td>
<td>[76]</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>a</td>
<td>[79]</td>
</tr>
<tr>
<td>TRAIL ligand</td>
<td>a</td>
<td>[78]</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>b</td>
<td>[77]</td>
</tr>
</tbody>
</table>

* In vitro results.
* a In vivo results in combination with menadione.
* b In vitro results in cells loaded with ascorbic acid.
* c In vivo results.
* d In vivo results in combination with menadione.

3. Clinical data

3.1. The first (disappointing) clinical studies

Fifty years ago, McCormick, a Canadian physician, observed that the generalized stromal changes of scurvy are identical to the local stromal changes observed in the immediate vicinity of invading neoplastic cells. Following his observations, he formulated the hypothesis that cancer is a collagen disease, secondary to vitamin C deficiency [90]. This hypothesis was
supported by the observation that patients suffering from advanced cancer generally present low concentrations of ascorbic acid in plasma [94]. However, this common deficiency is mainly correlated to the low dietary intake presented by these patients [92,93].

Twenty years after McCormick, Pauling and Cameron proposed the use of vitamin C supplementation in large doses for the prevention and treatment of cancer [94]. The treated group of Cameron and Pauling consisted of patients who were taking 10 g of ascorbate/day (intravenously for about 10 days and orally thereafter), at the time in the progress of their disease when the considered opinion of independent clinicians the continuance of any conventional form of treatment would offer no further benefit. The two controlled retrospective studies published in 1976 and 1978 showed that the mean survival times were, respectively, more than four and three times as great for the ascorbate subjects as for the controls [95,96]. Explaining these results, they postulated that the dangerous features of neoplastic cell (invasiveness, growth, etc.) were caused by matrix destabilization allowing the spread of cancer cells. This matrix degradation occurring in cancer neighborhood was thought to be the cause of collagen instability, itself due to a lack of hydroxylation of proline and lysine provoked by ascorbate depletion. Therefore, Pauling and collaborators were convinced that high doses of ascorbate would increase the formation of collagen, leading to tumors encapsulation. Rapidly, several criticisms were raised about the design of the Pauling/Cameron studies since they were not randomized or placebo controlled [97,98]. Actually, the ascorbate treated group was compared to 1000 retrospective controls whose records were obtained from the same hospital. These control patients suffered from similar diseases but did not receive ascorbate or other anticancer treatment. Furthermore, the average time from the initial diagnosis to “untreatable” status was not the same in the two groups, leading to an earlier “untreatable” labeling for Cameron’s patients. In an attempt to either duplicate or refute the amazing results obtained by Pauling and Cameron, the Mayo Clinic initiated different controlled double-blind studies. All concluded that high doses of vitamin C, when given orally, are not effective against advanced malignant disease [99,100].

3.2. New pharmacokinetic data and future directions

Since Pauling and Cameron’s studies, our current knowledge on the pharmacokinetics and pharmacodynamics of ascorbic acid provides the rationale to support its re-evaluation as adjuvant treatment for cancer patients [19]. Indeed, ascorbic acid is cytotoxic against a wide variety of cancer cells but presents a low toxicity towards normal cells, which could lead to consider ascorbate as an interesting anticancer agent [33,38,42]. However, the problem remained to achieve in vivo the cytotoxic concentrations described in vitro. As previously explained (Section 1.2), pharmacokinetic studies have clearly shown that ascorbate concentrations in plasma and tissue are tightly controlled as a function of oral dose. As a consequence, the oral administration of vitamin C cannot achieve plasma concentrations higher than 50–100 μM [5,6]. Thus, it should be noted that the original studies of Pauling and Cameron used i.v. and oral ascorbate, but the subsequent double-blind placebo-controlled studies used only oral ascorbate. This fact is probably not the only element that explains differences between the results of each study, but it could have a critical importance given the particular pharmacokinetic of ascorbic acid.

The follow-up studies to those of Cameron and Pauling aim now to administer high doses of ascorbate (30–60 g) by intravenous infusions [32]. This route of administration bypasses tight control and produces plasma concentrations up to 20 mM which are more than 100-fold greater than those produced by maximal oral dosing. Despite the fact that such concentrations are clearly cytotoxic for cancer cells in vitro, there is a paucity of clinical studies (mainly consisting in case reports) using such amounts of ascorbic acid in advanced cancer patients. In 2003, Drisko et al. have described the cases of two patients suffering from advanced epithelial ovarian cancer (stage IIIC for both) who underwent surgery and received standard chemotherapy (consisting of carboplatin and paclitaxel) followed by intravenous injections of ascorbic acid at 60 g, twice weekly during several months [101]. At the time of publication (40 months after the initial diagnosis), these patients presented no signs of disease and normal values of CA-125 antigen, the associated tumor marker. Given that the 5-year survival is of approximately 30% in the case of advanced ovarian cancers [102], these results suggest that ascorbic acid may improve the efficacy of chemotherapy. This study also demonstrates that i.v. administrations of vitamin C are relatively safe on the long-term. In 2006, Padayatty et al. reported three cases of patients suffering from different cancers who received intravenous injections of ascorbic acid (15–65 g once to twice per week for several months) [103]. These case reports were examined in accordance with National Cancer Institute (NCI) Best Case Series guidelines, a protocol which ensures a critical review. On the contrary of Drisko’s patients, the patients described in this second study declined conventional cancer treatment and instead chose to receive high dosage of vitamin C. For all these patients, a complete remission occurred and two of them were still alive 10 years after diagnosis, in good health. Although these case reports suggest that i.v. ascorbate might have a role in treating some cancers, it should be underlined that none of the cases presented in these two studies provides definitive proof that vitamin C was responsible for the patient’s favorable clinical course. Indeed, there is still the possibility that these cases are explained by spontaneous remissions. Furthermore, these patients were also taking other alternative medicine therapies such as oral antioxidants, minerals or plant extracts.

Actually, the concept of i.v. administration of vitamin C as a new adjuvant therapy remains controversial in the absence of solid clinical data. Fortunately, phase I and II clinical trials are now ongoing in patients with solid tumors. Their purpose is to document the safety as well as the clinical consequences of i.v. ascorbic. In the first phase I trial published this year, doses up to 1.5 g/kg have been injected i.v. to cancer patients with minimal adverse effects [104]. This protocol achieved plasma ascorbic acid concentrations > 10 mM for more than 4 h, which is largely sufficient to induce cancer cell death in vitro. However, no objective antitumor response was reported in this trial, likely because patients were suffering from multiply treated advanced cancer. This absence of apparent response is
consistent with what is observed in preclinical models of mice bearing human tumor xenografts since the parenteral administration of high doses of ascorbate decreased but did not suppress tumor growth [38]. Taken together, these preliminary data suggest that ascorbic acid alone is certainly not a miracle-pill. Further clinical studies are therefore warranted to define its putative value in cancer therapy, especially when it is used in combination with other cytotoxic agents, as reported by several studies [30,67-74,76,105]. It should be underlined that high doses of ascorbic acid may potentially induce some adverse effects even if ascorbic acid is generally perceived as free of toxicity. For instance, concentrations reached i.v. can trigger hemorrhology in patients suffering from glucose-6-phosphate dehydrogenase deficiency [106]. Since oxalic acid is a major end metabolite of ascorbic acid oxidation, hyperoxaluria has been frequently reported after its i.v. administration [107]. Ascorbic acid may also lead to urine acidification that could promote precipitation of urate, cystine, oxalate stones or drugs in the urinary tract [108]. Taken together, these data highlight the fact that i.v. injections of ascorbic acid should be considered as every other drug candidate as having potential side effects, thus requiring a medical environment and trained professionals.

4. Conclusion

Since its discovery 80 years ago, ascorbic acid has been one of the most popular chemical whose the beneficial effects are almost universally recognized. This popularity relies on one hand to common sense since ascorbic acid is associated with fruits and vegetables, known to be healthy, and on the other hand to expensive advertising campaigns which claim unproved benefits of vitamin C-based products. Preclinical studies suggest that ascorbic acid may have interesting anticancer properties, especially given the fact that some tumors may present an altered redox status. Furthermore, recent pharmacokinetic data demonstrate that oral and i.v. ascorbate administration are not comparable, the latter being the only route of administration allowing plasma concentrations thought to have pharmacological actions. Ascorbate was dismissed as a therapeutic agent in cancer treatment, but its use continues by some practitioners. Although ascorbic acid is generally perceived as non-toxic, its intravenous administration requires a professional medical environment.

It is striking to observe that an extensive literature exists on the use of vitamin C in cancer but finally no clear answer has yet been raised about its putative anticancer action in humans. Actually, the research on megadose vitamin C is an excellent example of controversial studies generated by inappropriate early-phase research [109]. It is to be hoped that further clinical trials will yield more information about the safety and the efficacy of high-dose i.v. ascorbic acid.

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