

# Vitamin C and Chemotherapy

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## Introduction

A recent paper by Heaney et al. (2008) claims that “vitamin C” antagonizes the cytotoxic effects of chemotherapeutic drugs.<sup>1</sup> On closer examination, the evidence presented does not support the claim. Contrary to Heaney’s suggestions, vitamin C is an effective anticancer agent, capable of killing cancer cells at concentrations achievable by oral supplementation.<sup>2</sup> Other researchers argue that vitamin C enhances the effectiveness of chemotherapy and curbs its side effects.<sup>3</sup> To understand these apparent contradictions, we need to appreciate the differing roles of vitamin C in the body and in tumors.

## Ascorbate and Dehydroascorbate

Vitamin C is a simple chemical, called ascorbate or ascorbic acid. Ascorbate is an antioxidant: each molecule can donate two electrons, helping to prevent free radical damage in the body. When ascorbate (vitamin C) donates its two electrons, it is oxidized to a different molecule, called dehydroascorbate.

In their experiments, Heaney et al. used dehydroascorbate or oxidized vitamin C, rather than ascorbate. Dehydroascorbate is an oxidant: it tends to gain electrons. Inside cells, dehydroascorbate molecules can be reduced back to ascorbate, by gaining electrons, produced using the cells’ metabolic energy. In tissues, this expenditure of cellular energy may add to the stress on sick cells, which typically exist in an oxidizing environment, under free radical attack.<sup>4,5</sup>

Vitamin C (ascorbate, antioxidant) has low toxicity, whereas dehydroascorbate (oxidized ascorbate, oxidant) is more toxic. Importantly, these two molecules can influence cancer cells in contrasting ways.

## Ascorbate and Cancer

Vitamin C can act as an anticancer agent, killing cancer cells by generating hydrogen peroxide and other oxidants. In tumors, vitamin C acts as an oxidant, rather than an antioxidant. Together with free iron or copper, the vitamin C causes a redox cycling Fenton reaction, which releases a cytotoxic oxidant, hydrogen peroxide. Many other substances, such as alpha-lipoic acid, vitamin K3, or the drug motexafin gadolinium, work similarly with vitamin C to generate oxidation and kill cancer cells.

## Dehydroascorbate and Cancer

In healthy individuals, the body maintains low dehydroascorbate levels, to minimize toxicity. When dehydroascorbate is formed, cells take it up and reduce it back to ascorbate. Thus, in healthy individuals, the level of dehydroascorbate is low, relative to the amount of ascorbate.<sup>6</sup> People taking vitamin C supplements consume ascorbate, not dehydroascorbate.

Researchers have suggested dehydroascorbate for use as an anticancer agent. To quote a recent paper, the results of studies on the effects of dehydroascorbate as an anticancer agent are “truly remarkable.”<sup>8</sup> Dehydroascorbate is selectively toxic to cancer cells.<sup>7,8</sup> Its effectiveness has been demonstrated both *in vitro*,<sup>9</sup> and in animal studies. In standard survival studies (using mice with P388 and Ehrlich carcinoma), 50 control mice received saline injections and had an average life expectancy of 11 days. Fifty experimental mice received 2 mg of dehydroascorbate (80 mg/kg) and lived for a minimum of 31 days; half of these had no detectable tumor cells and went on to survive long term.<sup>10</sup>

These dehydroascorbate results, like those on vitamin C itself,<sup>11,12</sup> put chemo-

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therapy to shame. In such experiments, even with aggressive conventional chemotherapy, an increase in life expectancy of about 2 days would be considered significant;<sup>13</sup> long term survival is rare.<sup>8</sup>

In another study, researchers investigated the effects of dehydroascorbate on the growth of solid tumors (Krebs 2 sarcoma and Ehrlich carcinoma). Control mice with Ehrlich carcinoma had an average tumor size of more than 2 cm<sup>2</sup>, whereas the subject mice, treated with injections of dehydroascorbic acid (2 mg per day about 80 mg/kg), developed no obvious tumors. In the control group, the Krebs sarcoma tumors were on average larger than 1.6 cm<sup>2</sup>, yet of those in the dehydroascorbate treated group, only two of 25 mice developed detectable (small) tumors.<sup>14,15</sup>

Animal studies have shown dehydroascorbate to be an effective anticancer agent, at doses lower than those for vitamin C.<sup>16</sup> These results were considered so unusual by an establishment accustomed to the failure of standard chemotherapy, that they were considered suspect and ignored. However, continuing research into ascorbate and dehydroascorbate as anticancer agents confirms their potential.

John Toohey has recently suggested a mechanism of action for the inhibition of cancer cells by dehydroascorbate. Toohey proposes that cancer cells synthesize homocysteine thiolactone, which reacts with dehydroascorbate to produce the toxic mercaptopyropionaldehyde. Cancer cells have an increased demand for methyl groups, which leads to homocysteine formation. This methylation is combined with a high rate of protein synthesis necessary for growth. Both these processes lead to homocysteine thiolactone and a susceptibility to dehydroascorbate toxicity.

#### **Dehydroascorbate is Not Vitamin C**

In the study by Heaney et al.,<sup>1</sup> the authors assume that giving an injection

of dehydroascorbate is equivalent to giving vitamin C; this is incorrect. In healthy tissues, high levels of dehydroascorbate are toxic and generates oxidative stress, whereas ascorbate's antioxidant action prevents such stress.

Within cancer tissues, the action of the two molecules is also different. Dehydroascorbate is absorbed rapidly by the cancer cells, where it may be reduced to ascorbate, through use of metabolic energy.

By contrast, ascorbate often remains in the extracellular space, where it takes part in a redox cycle, generating dehydroascorbate, hydrogen peroxide, and hydroxyl radicals. This results in oxidative damage to the cancer cells, which is cytotoxic.<sup>12</sup> In addition, the resultant dehydroascorbate may be taken up by the cancer cells and reduced, placing additional oxidative stress on the tumor.

#### **Poor Experimental Methods**

In the Heaney et al. paper, the researchers gave high doses of dehydroascorbate to cancer cells *in vitro*. The cancer cells absorbed the dehydroascorbate, reduced it internally, thus accumulating high levels of intracellular ascorbate (vitamin C). Our microevolutionary model<sup>17</sup> predicts that such levels of ascorbate could protect cancer cells from further stresses, such as chemotherapy. The intracellular ascorbate would lessen the occurrence of apoptosis, and might potentially aid cancer growth. However, these findings have no relevance to the use of ascorbate as an anticancer agent, nor do they suggest, as Heaney et al. argue, that high intakes of vitamin C are contraindicated during conventional chemotherapy.

Normally, the body maintains relatively high levels of ascorbate, compared to dehydroascorbate. In tumors, ascorbate is converted to dehydroascorbate, in a mechanism that generates hydrogen peroxide and hydroxyl radicals. This produces severe oxidation, which destroys cancer

cells by apoptosis and other mechanisms. Thus, high levels of ascorbate lead to an environment that is toxic to cancer cells. Once this poisonous environment exists, cancer cells may absorb the dehydroascorbate. However, reducing it back to vitamin C adds a second oxidative stress, taking energy from the cellular metabolism.

Thus, high levels of ascorbate do not act as antioxidants in tumors, but as oxidants, in a process that adds an additional selective stress to the tumor as it undergoes chemotherapy. Rather than acting as an antioxidant against the chemotherapy, as suggested, high levels of ascorbate should be synergistic with it. This action has been demonstrated in previous studies.<sup>18-23</sup> In their study, Heaney et al. circumvented the cytotoxic vitamin C Fenton reaction process, by using dehydroascorbate rather than ascorbate. Their study therefore has little relevance to the use of ascorbate as an anticancer agent.

### Inconsistent Results

In their mouse experiments, Heaney et al. report no appreciable anticancer effects with dehydroascorbate at a dose of 250 mg/kg. However, reports in the literature have demonstrated that, in mice, 300 mg/kg doses have a “truly remarkable” antitumour effect.<sup>8</sup> In some animal studies, dehydroascorbate appears to outperform standard chemotherapeutic approaches. The paper by Heaney et al. is inconsistent with these earlier animal studies, which are not cited in the paper.

### Conventional Chemotherapy is Generally Ineffective

Conventional chemotherapy has had some success in Hodgkin's disease, acute lymphocytic leukemia, testicular cancer, choriocarcinoma, retinoblastoma, and Wilm's tumor. However, these rare forms account for less than 5% of cancers in the United States. In the majority of cancers, there is little evidence that chemotherapy

extends life substantially.<sup>24</sup> The contribution of chemotherapy to survival is approximately a 2% increase (treated versus untreated patients).<sup>25</sup> The cost of this is high, both financially and in terms of reducing the quality of remaining life. Given such poor therapeutic results, oncologists should ask themselves why they continue to encourage patients to accept chemotherapy and yet ignore the potential benefits of vitamin C based redox therapy.

### Conclusions

The literature on the use of antioxidants in combination with chemotherapy or radiotherapy for cancer is complicated by the dual antioxidant/oxidant nature of many supplements. We can explain these inconsistencies in light of the redox microevolutionary model. There are numerous “antioxidants”, like vitamin C, which, at high intakes, can assist the cytotoxic mechanisms of conventional treatments, while protecting healthy cells from bystander toxicity.<sup>12</sup>

However, in the light of the fascinating experimental, animal and clinical data for the efficacy of an orthomolecular approach to cancer therapy, the crucial question is, why is this data being ignored? Rather than being welcomed, the topic appears to attract biased studies, apparently designed to show that vitamin C is not absorbed, is ineffective, or is harmful.<sup>4</sup>

The paper by Heaney et al. confuses dehydroascorbate with vitamin C. It bypasses the existing literature on dehydroascorbate, and fails to highlight that its results conflict with the literature on the action of both ascorbate and dehydroascorbate as cytotoxic anticancer agents. Furthermore, the paper shows little understanding of the oxidant role of high levels of vitamin C in tumors.

When the limitations of authors' interpretation of this paper are understood, the claim that vitamin C should not be taken by patients undergoing cancer is clearly

false and misleading. Unfortunately, if taken seriously, the Heaney et al. paper could stop cancer patients benefiting from the selective effects of redox therapy, including its lessening of side effects associated with the failed conventional approach to cancer chemotherapy. We can find no scientific or ethical justification for claiming that vitamin C supplementation may be harmful to cancer patients.

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