Commentary

Reevaluation of Ascorbate in Cancer Treatment: Emerging Evidence, Open Minds and Serendipity

Key words: cancer, ascorbate, plasma concentration, intravenous, cytotoxicity, vitamin C

Some clinicians and alternative therapy practitioners advocate megadose intravenous and oral ascorbate treatment of cancer. Randomized control studies using oral ascorbate showed no benefit. Recent data show that intravenous but not oral administration of ascorbate can produce millimolar plasma concentrations, which are toxic to many cancer cell lines. We propose that ascorbate treatment of cancer should be reexamined by rigorous scientific scrutiny in the light of new evidence.

Lack of vitamin C results in scurvy. Daily intake of 100 milligrams of vitamin C will prevent scurvy for one month if further ingestion ceases. However, optimum requirements of vitamin C for good health are unknown. This has led to wild speculations about the benefits of ascorbate, and enthusiasts still advocate daily intake ranging from hundreds to thousands of milligrams. At different times ascorbate was held to be beneficial for the common cold, strengthening the immune system, stress, depression, atherosclerosis and cancer prevention. At best, data supporting such benefits are incomplete. Nevertheless, vitamin C is widely used by the public, probably with little harm [1].

In this speculative sense, ascorbate is one of the early unorthodox therapies for cancer, based on two hypotheses but without supporting data. Nearly 50 years ago McCormick postulated that ascorbate protects against cancer by increasing collagen synthesis [2,3]. In 1972, Ewan Cameron hypothesized that ascorbate could have anti-cancer action by inhibiting hyaluronidase and thereby preventing cancer spread [4]. These hypotheses were subsequently popularized by Cameron and Linus Pauling [5,6]. Cameron and Campbell initially published case reports of 50 patients, some of whom seemed to have benefitted from high dose ascorbate treatment [7]. Although the rationale was not clear, intravenous as well as oral ascorbate was used in most patients. Cameron and Pauling then published the results of 100 patients with terminal cancer, in whom conventional therapy was no longer considered useful, and who were treated with 10 g ascorbate intravenously for 10 days followed by 10 g orally indefinitely. These patients included the previously reported 50 patients and 50 more who were randomly selected from a larger pool of patients who had received ascorbate treatment at the Vale of Leven District General Hospital in Scotland. The ascorbate treated patients were compared to 1000 retrospective controls who had similar disease but did not receive ascorbate or any other definitive anti-cancer therapy. Patients who received ascorbate survived 300 days longer than controls [8,9]. A prospective study was then conducted at the same hospital and two neighboring hospitals from 1978 to 1982. Results of 294 patients treated with ascorbate and 1532 controls were reported. Patients were not randomized but received ascorbate or palliative therapy, depending on the admitting physician. Treated patients had a median survival of 343 days against 180 days for controls [10]. Smaller studies have also reported benefits of ascorbate [11,12]. Ascorbate increased survival and well-being, and reduced pain. However, none of these studies were randomized or placebo controlled. Consequently, they have not been accepted by the scientific community. To test whether ascorbate was effective, Charles Moertel of the Mayo Clinic conducted two randomized placebo controlled studies of a hundred patients each with advanced cancer. Patients randomized to the treatment group were given 10 g of oral ascorbate, and neither study showed any benefit [13,14].

Because Moertel's studies were taken as definitive, ascorbate treatment was considered useless. However Moertel's results were not comparable to those of Cameron, as ascorbate was given orally and not intravenously. In retrospect, the route of administration may have been key [15]. While Pauling [16] and Cameron [17] objected to patient selection and other aspects of Moertel's trial, they may not have fully appreciated the critical difference between intravenous and oral administration.

Emerging knowledge suggests that the role of ascorbate in cancer treatment should be reexamined. The evidence falls into two categories: clinical data on dose concentration relationships and laboratory data describing potential cell toxicity at high concentrations of ascorbate in cell lines. Clinical data show that when ascorbate is given orally, fasting plasma concentrations are tightly controlled at <100 μM [18]. As doses exceed 200 mg, absorption decreases, urine excretion increases, and ascorbate bioavailability is reduced [15,18]. In contrast,

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when 1.25 grams of ascorbate are administered intravenously, concentrations as high as 1 mM (1000 μM) are achieved. The administered ascorbate is cleared within a few hours. Some clinicians have infused more than 10 g of ascorbate in cancer patients and achieved plasma concentrations of 1 to 5 mM [19]. However, their call to restudy its effect in cancer using intravenous ascorbate has gone unheeded [19]. It is now clear that intravenous administration of ascorbate can yield very high plasma levels, while oral treatment does not. Reported complications of intravenous ascorbate are unusual. These include rare cases of hemolysis in patients with G6PD deficiency and oxalate nephropathy [1]. Adverse effects may occur in patients with iron overload and renal failure.

Laboratory data show that ascorbate is toxic to a variety of cancer cell lines [20–22]. Extracellular concentrations as low 100–200 μM are toxic to some cell lines, but many types of malignant cells are killed only at concentrations approaching the mM range [19]. Although ascorbate toxicity to cancer cells appears to be a result of high extracellular, rather than high intracellular concentrations, the mechanism of toxicity is unknown [23]. Possibilities include stimulatory effects on apoptotic pathways, accelerated pro-oxidant damage that cannot be repaired by tumor cells and increased oxidation of ascorbate at high concentrations in plasma to the unstable metabolite dehydroascorbic acid, which in turn can be toxic. It remains possible that toxicity is an artifact of cell culture [24], perhaps due to contamination of media by iron [25] or other cations resulting in excessive oxidation. Nevertheless, concentrations that cause toxicity to cancer cells *in vitro* can be achieved clinically by intravenous, but not oral, administration of ascorbate.

Some clinicians have treated patients with terminal cancer using high dose intravenous ascorbate, often with other nutritional supplements or other alternative therapies. Nevertheless, patients are receiving high doses of intravenous ascorbate now. What is lacking is a study of cases with well-documented pathology. The observed outcome should be compared to the expected outcome, to show whether ascorbate has any benefit. If unambiguous benefit can be shown even in a few cases, the use of ascorbate should be explored in more controlled studies. After all, even a small benefit is worthwhile as ascorbate is nontoxic and inexpensive, in contrast to the many chemotherapeutic agents in use. If the results show a clear lack of benefit, the use of ascorbate as a chemotherapeutic agent in cancer should be abandoned.

We now know that intravenous, but not oral ascorbate produces a high plasma concentration in the range at which it is toxic to some tumor cells. It is time to review ascorbate's efficacy as an anticancer agent, when administered intravenously in large doses, as reported in the studies by Cameron, Campbell and Pauling. The hypotheses are unproven that ascorbate results in hyaluronidase inhibition and strengthening of the intercellular matrix, but ascorbate may have anti-cancer actions through entirely unrelated mechanisms. The role of serendipity in science should not be underestimated. In cancer treatment we currently do not have the luxury of jettisoning possibly effective and nontoxic treatments. We should revisit promising avenues, without prejudice and with open minds [26], and conduct studies without allowing desperation to diminish scientific rigor.

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