

## Comment re: Vitamin C Antagonizes the Cytotoxic Effects of Chemotherapy

### To the Editor:

On the basis of cell and animal experiments with dehydroascorbic acid, Heaney and colleagues state, "These results suggest that supplementary vitamin C may have adverse consequences in patients receiving cancer therapy" (1). Selectively referring to dehydroascorbic acid as vitamin C throughout the majority of this work may send a clouded message to patients and their caregivers. All known actions of vitamin C are mediated by the reduced molecule ascorbate, not the oxidized molecule dehydroascorbic acid. Mice lacking the tissue transport protein specific for ascorbate (Slc23a2) do not survive because of severe vitamin C deficiency, despite having no impairments in dehydroascorbic acid transport (2).

The suggestion that "...study conditions were relevant to clinical conditions" (1) should be viewed cautiously. Compared with cells devoid of any ascorbate, researchers attenuated cytotoxicity to antineoplastic agents *in vitro* (11-27%) by prior treatment with 500  $\mu\text{mol/L}$  dehydroascorbic acid, which rapidly elevated intracellular ascorbate concentrations up to 18  $\text{mmol/L}$  within 1 hour (1). *In vivo*, numerous reductive systems ensure plasma concentrations of dehydroascorbic acid do not exceed 1  $\mu\text{mol/L}$  (3, 4). Although alluded to, the actual level of dehydroascorbic acid formed endogenously within the oxidative environments of tumors was not measured in either this (1) or the previous studies cited by this group (5, 6). Most cells *in vivo*, including cancer cells, maintain a constant intracellular ascorbate concentration of 1 to 5  $\text{mmol/L}$ , which never decreases to zero. Data collected *in vitro* by comparing two extremes, 0 and 18  $\text{mmol/L}$  ascorbate for instance, are implausible with regard to tumors and other tissues in general. The investigators conclude that "This finding could have important clinical relevance given the wide use of vitamin C as a nutritional supplement" (1). However, to produce an effect in xenografted mice, a course of  $8 \times 250 \text{ mg/kg}$  dehydroascorbic acid was administered intravenously (1). This regimen does not simulate oral ingestion of vitamin C supplements. In fact, irreversible diabetes can be induced in rats after intravenous injection of 700  $\text{mg/kg}$  dehydroascorbic acid (7).

Because meaningful differences exist in regard to chemistry, bioavailability, and metabolism, it may be imprudent to connect data gathered with dehydroascorbic acid to vitamin C (ascorbate) and oral supplements. Numerous randomized human clinical trials have not shown decreased chemotherapeutic efficacy with dietary supplement usage, including vitamin C (8). Scientific dialogue on the subject may benefit from further preclinical testing of oral vitamin C (ascorbate) supplementation and cancer treatment in addition to experiments designed solely with dehydroascorbic acid.

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### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### References

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