LETTER

Mega-dose vitamin C as therapy for human cancer?

Frei and Lawson (1) paint a rosy picture of the potential of vitamin C as therapy for human cancer. The authors are located at the Linus Pauling Institute and therefore are in a special position to revitalize the interest in vitamin C promoted by the articles of Cameron and Pauling in PNAS 30 years ago; however, the evidence that vitamin C could help human cancer patients is still thin.

1. Chen *et al*. (2) find that megadose i.p. vitamin C results in an ≈2-fold growth decrease of a human (Ovcar 5), a mouse (PanO2), and a rat (9L) tumor xenografted into immunocompromised mice. Although this growth retardation is significant, the effect is modest. Standard chemotherapy shrinks such tumors more effectively. It would have been more useful to test the vitamin C in one of the "spontaneous" tumors now available in genetically modified mice. These resemble human tumors more (3).
2. Although it is interesting that huge vitamin C concentrations generate H_2O_2 that kills tumor cells (2), there is a long history of compounds generating oxidative stress that were tested in cancer therapy but did not make it. Plumbagin, the hydroxyl analog of menadione (vitamin K precursor), and menadione itself are examples (see refs. 4–9). Chen *et al*. (2) have not tested whether vitamin C is superior in their model system to the older oxidative stress generators.
3. Frei and Lawson (1) discuss the papers by Cameron and Pauling in PNAS that led to their conclusion "that treatment with ascorbate in amounts of 10 g/day or more is of real value in extending the life of patients with advanced cancer" (10). Frei and Lawson (1) stress the high statistical significance of the positive effect of vitamin C. They dismiss the solid refutation of the conclusions of Cameron and Pauling (summarized in ref. 11) by emphasizing that Cameron and Pauling (10) used i.v. and oral vitamin C, whereas the later trials used only oral vitamin (11). They failed to mention, however, that the vitamin C was at best given for only 10 days i.v. and that the 10-g dose must have been insufficient to reach the plasma levels (12) now considered necessary for a substantial antitumor effect of vitamin C (1). They also fail to mention that the Cameron–Pauling trial was considered uninterpretable by oncologists because of biased patient selection.
4. Frei and Lawson (1) state that "a series of case reports indicated that high-dose vitamin C was associated with long-term tumor regression in three patients with advanced renal cell carcinoma, bladder carcinoma, or B cell lymphoma" (13). They fail to refer, however, to an editorial in the same journal titled "High-dose vitamin C therapy: Renewed hope or false promise?" (14), in which the authors point out the pitfalls of such case reports: "However, these are only 3 individual cases of very different types of cancer, and in each case there is a possible alternative explanation for the positive outcome. . . . Finally, these case reports omit the number of patients who received high-dose intravenous vitamin C therapy with no effect. Because these cases were collected over many years from several institutions, this number may be quite large and the overall response rate quite low" (5). Frei and Lawson (1) also refer to the "remarkable tolerance for high-dose i.v. vitamin C" in a phase I trial in selected cancer patients (12) but fail to mention the conclusion of this trial: "No patient experienced an objective anticancer response . . ." (12).

It is possible that "the promise of ascorbic acid in the treatment of advanced cancer may lie in combination with cytotoxic agents" (12). As long as this has not been tested, we should try to avoid a new hype of vitamin C as cancer treatment by pointing out, especially in PNAS, the limitations of the available data.

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