Review of: "Ascorbic Acid Therapy in Hematological Malignancies - The Current Knowledge and Future Directions"

Jonathan Nyce

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Review of “Ascorbic Acid Therapy in Hematological Malignancies - The Current Knowledge and Future Directions,” by Yam, Ha and Yip.

Anthropoid primates lost the capacity for de novo synthesis of vitamin C approximately 56 million years ago, during the Paleocene Eocene Thermal Maximum (PETM), as a result of Alu transposon-mediated inactivation of the Gulonoloactone Oxidase (GLO) gene, the rate limiting step of ascorbate synthesis. GLO inactivation has been retained in the anthropoid lineage for the entire 56-million-year subsequent years, revealing that it enabled some aspect of speciation in the primate lineage, or GLO activity would have been restored. What this function in speciation might be has been a puzzlement among biologists for decades.

In the early 1980s, this reviewer attended a debate between his mentor, Sydney Weinhouse, and Linus Pauling— a double noble laureate, and fierce proponent of extremely high dose ascorbic acid (vitamin C) for the prevention of cancer. The subject of human consumption of high dose ascorbic acid was in fact the subject of the debate, with Pauling arguing that extreme high dose *oral* ascorbic acid had cancer chemo preventative action. Professor Weinhouse argued the counterpoint, that the loss of the ability to synthesize ascorbate has been retained throughout the anthropoid primate lineage speciation for a reason, even though he could not, at that time, provide any indication of what function the loss of ascorbate synthesis might enable. Unfortunately, Linus Pauling died of cancer in 1994. Sidney Weinhouse also died of cancer, in 1991.

In the 1970s, Cameron and Pauling described patients with advanced cancer who had survival benefit and symptomatic relief using high dose ascorbate (10 g/day) (Cameron and Campbell, 1974; Cameron and Pauling, 1976; Cameron and Pauling, 1978). However, two rigorous double-blind placebo-controlled prospective trials were subsequently performed at the Mayo Clinic using the same dose of ascorbate failed to confirm these results. Oral ascorbate as an anti-cancer agent was subsequently dismissed (Creagan et al., 1979; Moertel et al., 1985; Wittes, 1985). Is there an explanation for these disparate results? Whereas Cameron administered 10 grams ascorbate intravenously as well as orally in his studies, the Mayo investigators used oral ascorbate only.

Subsequent studies revealed that vitamin C showed efficacy only after the high blood concentrations possible with

intravenous dosing were employed (1g/kg over 90–120 minutes two to three times weekly). At such concentrations, vitamin C acts as a prodrug for hydrogen peroxide (Chen et al., 2005; Chen et al., 2007). Such pharmacologic doses of vitamin C were reported to be selectively toxic to tumor cells in vitro and in vivo (Chen et al., 2005; Chen et al., 2008; Verrax and Calderon, 2009). Importantly, there are no data showing that pharmacologic ascorbate interferes with chemotherapy.
There is limited information suggesting that intravenous vitamin C may improve time to relapse and enhance reductions in tumor mass and improve survival in combination with chemotherapy.

In this manuscript under consideration at Queios, “Ascorbic Acid Therapy in Hematological Malignancies - The Current Knowledge and Future Directions,” by Yam, Ha and Yip, summarizes the work that has been used employing extreme high dose iv ascorbic acid in the treatment of hematopoietic cancers.

This is a well written mini-review that would benefit from deeper analysis of the studies discussed. For example, a two-line paragraph on administration of antioxidants (presumably in the case of therapeutic overdose) is particularly uninformative. I would encourage the authors to be more thorough in their discussion of the various topics undertaken related to high dose ascorbate treatment in cancer.

In summary, this is an important area of research, and while there are several excellent reviews already in the literature on this subject (e.g., Mehdi et al, 2021; Kazmierjac-Baranska et al, 2020).

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