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

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Potential competing interests: The author(s) declared that no potential competing interests exist.

The work presented for review is very informative and carrying content that would seem to be well known for years, but still require clarification.

I think it can not be published as long as the authors will take a stance on the comments below:

- *"The difference is due to a tight regulatory mechanism of AA uptake by sodium vitamin C cotransporter (SVCT) 1 in small intestine which could be bypassed with IVAA.[7]"* - I am asking for a more detailed and broader commentary on this task.
- *"AA, at high concentration, acts as pro-oxidant by its ability to reduce Fe3+ to Fe2+, which accelerates the redox cycle of Fe3+ and Fe2+ in the Fenton reaction, with consequent generation of reactive oxygen species (ROS) including hydroxyl radicals and hydrogen peroxide (H_2O_2).[8][9][Fig3]"* - Fig3 is missing in the text. The extracellular ROS can induce cell damage by lipid peroxidation.- there is no reference to the subject literature in this case. I am asking for a more detailed comment on this task.
- *"Kawada et al.[13] found that the apoptosis of the leukemia cell lines induced by high-dose ascorbate (≥280 μM) was almost completely abrogated by the addition of catalase. These in vitro study results provided insight on the reason why patients are tolerating high-dose IVAA well in general."* - In my opinion, this explanation of tolerating high-dose IVAA is not enough. A more precise explanation would come in handy.
- *"Multiple studies have also shown that serum AA levels are significantly reduced in patients with hematological malignancies.[30][31][32]"* - The reference level of serum AA levels in healthy people should be given here, of course with reference to the literature on the subject.
- *"OAA supplementation was demonstrated to be associated with mildly increased risk of renal stone formation in men but not in women.[42]"* - it should be explained why this is so
- *"Oral prophylaxis with magnesium oxide and vitamin B6 could be considered in patients with history of calcium oxalate calculi formation.[44]"* - why is such supplementation recommended, please explain precisely
- *"The anti-cancer effect is largest when high-dose AA was administered to immunocompetent mice but not to immunocompromised mice, suggesting that AA has immunomodulatory function that requires an intact immune system to maximize its benefits.[63]"* - Such a statement without appropriate comment is illogical, because it is known that in cancer disease there is a reduced immunity. I am asking for a precise explanation

- *"There is also need to explore whether OAA could be used instead of IVAA in some circumstances."* - what are the circumstances according to the authors, please specify.
- *"The duration of exposure to a cytotoxic level of AA required to produce clinical benefits is uncertain. These factors should be considered to determine the optimal frequency of AA administration. Campbell et al.[26] showed that increased tumor ascorbate level could be maintained by daily administration of IVAA, even though plasma AA level would be normalized much earlier. The in vitro studies showed that the synergistic effects occur with low concentration of AA, therefore low to intermediate-dose of IVAA or high-dose OAA could potentially produce benefits[49][56][57]."* - in that case, please specify what, even theoretically, according to the authors, the potential doses should be given, together with the reference serum AA concentrations for healthy people.
- Finally, a practical note, please list all Abbreviations. at the beginning of work to facilitate reading.