The effects of vitamin E and selenium on cisplatin-induced nephrotoxicity in cancer patients treated with cisplatin-based chemotherapy: A randomized, placebo-controlled study

Sir,

We read with great interest the article by Hemati and colleagues, entitled "The effects of vitamin E and selenium on cisplatin-induced nephrotoxicity (CIN) in cancer patients treated with cisplatin (CP)-based chemotherapy: A randomized, placebo-controlled study," published recently in your esteemed journal.[1] They studied 22 patients, who received 400 IU vitamin E and 200 μg selenium daily and 24 patients received placebo. They found significant differences in glomerular filtration rate between the two groups after the third cycle and 1 month after the end of chemotherapy. They concluded that vitamin E and selenium can be used to reduce CIN. We congratulate the authors for their findings and their effort to find a way to reduce CIN. However, we would like to clarify a few points about CIN. In a preclinical study to find the protective role of endogenous nitric oxide donor (L-arginine) in CIN, we studied 33 Wistar rats and we found, L-arginine had protective effects against CIN in males, however, it promotes the induced damage in females. We concluded a gender related difference in rat model of CIN.[2] Likewise, to the study of Hemati *et al*., ameliorative effects of viamin E was also found in our another study on 32 Wistar rats.[3] We also showed the renoprotective effects of Losartan as an angiotensin II receptor 1 (AT1) blockade in CIN in rats.[3] Surprisingly, we also found a low dose of magnesium (Mg) supplementation intensifies kidney toxicity and renal dysfunction in CIN in the rat model. We concluded that, the protective role of Mg with moderate and high doses is not certain.[4] We also observed that co-administration of vitamin C and losartan was not more effective than the administration of vitamin C or Losartan alone.[5,6] While, the role of gender in CIN is not well known, we conducted a study on rat model of CP nephrotoxicity and observed, losartan may prevent CIN in males, but it promotes the CP-induced damage in females, which may be related to the renin-angiotensin system receptors in the kidneys.[7] Additionally, we recently reported that, vitamin E, vitamin C, or losartan is not nephroprotectant against CIN in presence of estrogen in ovariectomized rat model,[8] which is in agreement with our previous findings. More recently we observed that estrogen abolished protective effect of erythropoietin against CIN in ovariectomized rats,[9] while renoprotective effects of erythropoietin was also shown in our previous study.[10-13] Hence, it is well documented that there is a gender difference in the CIN in the rat model. It is documented that some cases of chronic renal diseases are gender related too.[13-19] Few studies published regarding the sex difference in CIN.[19,20] Hence, there still remains a number of big questions to further explore mechanisms interact in CIN. We propose to conduct clinical studies to understand the factor of gender difference in CIN.

Accordingly, in Hemati *et al*., study the distribution of gender was not specified. In our recent study (not publish data) the effect of vitamin E on CIN also was gender depended.

It is our pleasure to recommend some suggestions for further studies in this area;

- Selenium is a component of the antioxidant enzymes glutathione peroxidase and thioredoxin reductase. Vitamin E also is an antioxidant. In this study, both of this antioxidant were supplemented. Therefore, the positive reported results may obtain by one of each or both. On the other hand, antioxidants may have interaction too. So, we suggest single supplementation for such similar study
- As mentioned before, sex-based difference in CIN should be considered in similar studies. Sex hormone; estrogen may abolish the effect of antioxidant supplementation[8,9]
- Given more data for kidney functions such as blood urea nitrogen and creatinine, and also more data such as Malondialdehyde, superoxidase dismutase or glutathione to evaluate the oxidative stress is extremely important. Comparison these data before and after CP therapy will provide a better conclusion
- Using advance statistical analysis may provide more scientific conclusions about the effect of supplementation, and finally
- We have to be sure that antioxidant supplementation should not reduce the effect of CP on the tumor target. So special attention is needed for antioxidant selection, especially in clinical trials.

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