

Rebuttal letter

Title: Chemotherapy-induced neurotoxicity in the treatment of gynecological cancers. State of art and an innovative approach for prevention

Ester Oneda^{1*}, Chiara Abeni¹, Laura Zanotti², Elisabetta Zaina³, Sara Bighè³, Alberto Zaniboni¹

¹ Medical Doctor, Department of Clinical Oncology, Fondazione Poliambulanza, Brescia, Italy

² Data Manager, Department of Clinical Oncology, Fondazione Poliambulanza, Brescia, Italy

³ Nurse, Department of Clinical Oncology, Fondazione Poliambulanza, Brescia, Italy

*Corresponding Author: Ester Oneda, MD, Department of Clinical Oncology, Fondazione Poliambulanza Bissolati street 57, Brescia, Italy, 25124. Tel: 0303515557 E-mail: dott.ester.oneda@gmail.com

Answer Reviewer 1: Although chemotherapy and target therapies for cancer patients have brought enormous benefits in terms of treatment and prognosis, so far little has been done in reducing and preventing the side effects of the drugs used. In particular, some of these side effects have a significant impact on the patient's quality of life (QoL) [1, 2] and persist for a long time after the end of treatment. Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect that occurs in 20% of ovarian cancer patients treated with the combination of carboplatin and paclitaxel (CP) [3]. In this review, we summarize the evidence regarding the incidence of CIPN with different taxane formulations, regimen schedules and mechanical preventive systems. We provide the evidence regarding Hilotherm® Chemo care device, a regional cooling system that lowers the temperature of the hands and feet in order to prevent the onset of CIPN [4]. We show data from two studies and the updated data from 44 ovarian cancer patients treated with CP in our center. Our study has few limits: it is a single-arm trial without a direct comparator, the patients originate from a single center and the sample size was small. The strength of this study is that it used patient-reported toxicity outcome measures and the data reflect a real-world setting. But, as in the introduction of any new drugs/device in the anticancer treatment armamentarium, the modern research pathway has prior pilot study, followed by confirmatory larger studies and after that randomized clinical trials. With our experiences [4] we are just in the early stage of development of this new technique and we are simply provide the initial basis leading to future controlled clinical trials. In order to clarify the content of this review we modify the title and we add a special paragraph in the result section dedicated to the mechanical approach of CIPN prevention, as it was suggested by reviewer 1.

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere. We found the advices very appropriate and worthy of being followed for a better clarity of the manuscript. We hope the work rearranged in this way will find your approval.

We aimed to improve the quality of our paper. We hope that now it could be accepted for publication.

- [1] M. A. Bakitas, "Background noise: the experience of chemotherapy-induced peripheral neuropathy," (in eng), *Nurs Res*, vol. 56, no. 5, pp. 323-31, 2007 Sep-Oct 2007, doi: 10.1097/01.NNR.0000289503.22414.79.
- [2] C. Tofthagen, "Surviving chemotherapy for colon cancer and living with the consequences," (in eng), *J Palliat Med*, vol. 13, no. 11, pp. 1389-91, Nov 2010, doi: 10.1089/jpm.2010.0124.

- [3] J. R. Brewer, G. Morrison, M. E. Dolan, and G. F. Fleming, "Chemotherapy-induced peripheral neuropathy: Current status and progress," (in eng), *Gynecol Oncol*, vol. 140, no. 1, pp. 176-83, Jan 2016, doi: 10.1016/j.ygyno.2015.11.011.
- [4] E. Oneda *et al.*, "Innovative Approach for the Prevention of Chemotherapy-Induced Peripheral Neuropathy in Cancer Patients: A Pilot Study With the Hilotherm Device, the Poliambulanza Hospital Experience," (in eng), *Integr Cancer Ther*, vol. 19, p. 1534735420943287, 2020 Jan-Dec 2020, doi: 10.1177/1534735420943287.