Manuscript NO.: 34286

We would like to thank the Editor and Reviewers for the review of our manuscript # 34286.

We agree with almost all comments of the reviewers and have revised our manuscript according to their suggestions.

The English language editing was performed on our manuscript by a native English-speaking editor.

Responses to the Reviewer's comments and suggestions

Reviewer Id 02447901:

In this manuscript, the authors aimed to give a summarization and basic information of platinum-derived neurotoxicity. Although the heterogeneity in identity, several potential neurotoxic mechanisms were listed and described. As a clinically relevant issue, vulnerable population, clinical signs, action mechanisms, prevention, treatment, and alternative options are of importance. Thus, in addition to description of neurotoxic mechanisms, the information of any prevention and treatment strategies is also practical to the population of great interests. Besides, the structures of platinum drugs, metabolites, and DNA adducts are recommended to add.

Response and revision: We very much appreciate the reviewer's suggestions.

We added some informations about these important issues in the revised manuscript according to the suggestions of the reviewer as follows:

In the first paragraph, the structure of platinum drugs was summarized:

"Platinum drugs, including cisplatin (cis-diamminedichloroplatinum II), carboplatin (cis-diammine-1, 1-cyclobutane dicarboxylate platinum II), and oxaliplatin (trans-R,R-cyclohexane-1,2-diamineoxalatoplatinum II) have become an important part of the…"

The structure of DNA adducts was summarized on page 6:

"They usually form same types of adducts on the same DNA sites, including 1,2-intrastrand d(GpG) (between adjacent guanine bases on the same DNA strand) and 1,2-intrastrand d(ApG) (between adenine and adjacent guanine bases on the same DNA strand) crosslinks."

Vulnerable population was discussed on page 5:

"Some clinical and genetic features of patients may make them more susceptible to developing severe neurotoxicity during treatment with platinum drugs. A recent study by Velasco et al found that among patients treated with oxaliplatin-based chemotherapy, male patients, patients experiencing more severe acute neuropathic symptoms, patients with

abnormal findings on mid-treatment nerve conduction velocity studies, and patients receiving higher cumulative oxaliplatin doses have an increased risk of developing significant neuropathic symptoms [7]. Several recent pharmacogenomics studies have suggested that patients with polymorphisms in the Glutathione S-transferases genes (GSTM1, GSTT1, and GSTP1) are more likely to develop grade 3-4 cumulative neuropathy during oxaliplatin treatment due to decreased drug detoxification [8]."

Prevention and treatment strategies were discussed on pages 13 and 14:

"PREVENTION AND TREATMENT STRATEGIES

A recent Cochrane review examined the effects of the potential chemo-protective agents against neurotoxicity of platinum analogs [54]. This review included 29 randomized controlled trials (RCTs) and analyzed data from 2906 participants who received platinum-containing chemotherapy (cisplatin, carboplatin, or oxaliplatin) alone or in combination with a potential chemo-protectant, including amifostine, calcium/magnesium infusion, glutathione, Org 2766, acetylcysteine, oxcarbazepine, or vitamin E [54]. The data obtained in this study were found to be insufficient to recommend any particular agent to prevent or limit platinum drug neurotoxicity.

In 2014, the American Society of Clinical Oncology convened an expert panel to develop a clinical practice guideline for the prevention and treatment of chemotherapy-induced neuropathies in adult cancer survivors [55]. The experts reviewed 48 RCTs that investigated the efficacy of pharmacological agents, including antiepileptic drugs (carbamazepine and oxcarbazepine), antidepressants (amitriptyline, nortriptyline, venlafaxine and duloxetine), vitamins/minerals (calcium/magnesium infusions, vitamin E, and glutamine), and antioxidants (glutathione, N-acetylcysteine, and amifostine) against neuropathic pain caused by platinum compounds, paclitaxel or vinca alkaloids. They concluded that enough evidence to support routine clinical implementation of these agents for the prevention of platinum-induced peripheral neurotoxicity was not found. Conversely, duloxetine was found potentially useful for treating oxaliplatin-induced neuropathic pain."

Reviewer Id 3665523:

This is a concise and effective review article about the known mechanisms of platinum-induced neurotoxicity, but adding implications for clinical practice is strongly suggested to complete it. Are there any strategies for early recognition of symptoms? Which are the measures that can be used for treatment and follow up? Are there any future directions for improvememt of diagnosis and therapy?

Response and revisions*:* We very much appreciate the reviewer's suggestions.

We added some informations about these important issues in the revised manuscript according to the suggestions of the reviewer as follows:

We have discussed diagnostic methods and measures that can be used for treatment and follow-up on pages 12 and 13:

"DETECTION AND ASSESSMENT OF PLATINUM-INDUCED NEUROTOXICITY

Currently, no standard clinical method for the early detection and comprehensive assessment of platinum-induced neurotoxicity is known. The use of self-reporting questionnaires developed by the United States National Cancer Institute and European Organization for Research and Treatment of Cancer throughout the treatment course has been recommended as a simple clinical tool for determining and grading a pre-existing or new neuropathy [51,52]. These questionnaires contain items that evaluate the occurrence, severity, degree of distress, and frequency of neuropathic symptoms and their negative impacts on the patient daily activities.

Among neurophysiological techniques, nerve conduction velocity studies and electromyography remain the gold standard technique for detecting the location and extent of neuronal damage due to treatment with platinum drugs [1,6]. Nerve excitability studies performed before and immediately after oxaliplatin infusion have emerged as novel non-invasive tests for early identification of patients at high risk for severe neurotoxicity [35,53"

Possible treatment options were discussed as above mentioned.

Reviever Id 2279508:

The authors provide a list of known effects of platinum based cancer therapies that may contribute to their clinically important neurotoxicity. The contribution would be much greater if they would flush out the larger picture a little. For example, given this list of effects, which are likely to be most important to the clinical picture? Also, they point out that carboplatin is much less neurotoxic, Why? Does it containless platinum, or ... . Why do we not just use carboplatin? Is it not as effective? They really need to move a bit past a taxonomy lesson, a list of effects in the literature

Response and revisions: We very much appreciate the reviewer's suggestions.

We discussed this issue on page 4 as follows:

"Carboplatin neurotoxicity is negligible compared with that of cisplatin and oxaliplatin, however, it can develop, particularly high doses are administered [3,4]. Exposure of rat sensory neurons in culture to cisplatin, oxaliplatin or carboplatin in vitro caused a concentration-dependent increase in cell death and apoptotic cells [5]. However, carboplatin required a 10-fold higher drug concentration than cisplatin to induce a similar degree of cytotoxic effect. In addition, both cisplatin and oxaliplatin led to increased reactive oxygen species production and 8-oxoguanine DNA damage, but carboplatin did not [5]. These preclinical observations may partly explain why carboplatin has less neurotoxic effects."

We also made some changes in the "conclusion" part of the review, and revised it according to the new version of the manuscript.

CLOSING COMMENTS TO THE EDITOR

Again, we appreciate the opportunity to revise our manuscript for consideration for publication in WJCO. We hope our revision meet your approval.

Thank you,

Ozkan Kanat