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Correspondence

Comments on: Pharmacokinetics of cisplatin during open and minimally-invasive secondary cytoreductive surgery plus HIPEC in women with platinum-sensitive recurrent ovarian cancer: a prospective study

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Conflict of Interest
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The article by Petrillo and colleagues [1] recently presents the cisplatin (CDDP) pharmacokinetic profile in a prospective series of patients enrolled in the HORSE (NCT01539785) trial, a randomized controlled trial exploring the prognostic role of hyperthermic intraperitoneal chemotherapy (HIPEC) for women with platinum sensitive recurrent epithelial ovarian cancer treated with open secondary cytoreductive surgery (O-SCS) or minimally-invasive secondary cytoreductive surgery (MI-SCS). In this study, the authors highlight for the first time that MI route enhances CDDP peritoneal tissue uptake during HIPEC procedures.

Despite the initial enthusiasm with the findings of women receiving HIPEC through a MI approach reach double CDDP peritoneal tissue levels compared to patients submitted to O-SCS, we would like to add some criticism to this issue in light of previous experiences [2-4]. Firstly, some results presented for supporting the influence of surgical approach (i.e., O-SCS vs. MI-SCS) over the CDDP pharmacokinetic in women receiving SCS plus HIPEC are not clear. For example, since the CDDP dosage and the total volume of perfusate are quite similar in both groups according to table 1, why should we expect higher concentration of CDDP in the peritoneal perfusate over all the time during HIPEC in the MI-SCS group? Further, the minimal and non-significant difference between the groups in terms of plasma concertation from T20 to T60 associated to the statistically significant difference in the time point of T120 suggests the increased intra-abdominal pressure (IAP) by pneumoperitoneum during the "carefully re-exploration of the abdomen" in the MI-SCS, and not the MI route itself, might play a role for the higher concentration of CDDP in peritoneal tissue samples observed in this group. As previously reported, the patency of lymphatic stomata in the peritoneum can vary in response to lot of factors and thus, a high IAP could enhance the patency of these stomata and their ability of lymphatic absorption [5]. Accordingly, the residual dose of CDDP in the peritoneal

cavity after HIPEC when submitted to the effect of pneumoperitoneum during the short time of the laparoscopic re-exploration could be enough for enhancing concentration of CDDP in the peritoneal biopsies collected at the end perfusion.

Second, the practices of HIPEC are widely variable in terms of technical particularities and regimens of drugs, which may impact on patient outcomes, producing heterogeneous and no comparable results. Herein, a started point of discussion is performing HIPEC as a closed or open abdominal (coliseum) technique. Whilst there are no convincing data favoring any technique, the closed technique has been preferred in many centers based on the simplicity of this method and decreased contamination risk [2]. In these settings, a minimum of 4 L (ranging from 4 L to 6 L) of perfusate into the abdominal cavity has also been advocated in order to counterbalance the theoretical drawbacks of closed techniques in comparison to the open approach, since a maximal distention of the abdomen enhances the thermal homogeneity throughout the peritoneal cavity and facilitates drug distribution into the whole abdomen, ensuring that every site of the diffuse peritoneal disease receives the optimal treatment [2-4]. Despite a perfusate volume of 2 L/m^2 have proved to be appropriated for the open abdominal technique (Coliseum technique) [6], we are afraid it is not a good technical parameter for the closed approach, and thus the value of HIPEC could be underestimated in the HORSE trial, mainly in patients that underwent O-SCS. In line with the aforementioned arguments, some have chosen for the closed technique with perfusate volumes of 4–6 L, applying concentration-based intraperitoneal protocols instead of body surface area-based regimens of chemotherapy [3,7-9]. The peritoneal surface malignancy unit of Milan has recently demonstrated in a randomized phase II trial (NCT02949791) that increased IAP, achieved by increasing the total volume of perfusate, improves the peritoneal distribution of CDDP with no concerns related to safety [3]. These same concepts have been applied in another ongoing clinical trial (NCT02249013) exploring a comprehensive protocol including neoadjuvant chemotherapy, interval cytoreductive surgery, short-course HIPEC and fast-track recovery in patients suffering of advanced ovarian cancer [9]. In Petrillo et al.'s study [1], the IAP levels during HIPEC were not measured. Therefore, even though the study groups received equal amount of perfusate, the authors could not assume that HIPEC-IAP in both groups were similar since IAP is a function of several factors other than total amount of perfusate. We should consider the volume of remaining viscera after the cytoreduction and complacency of the abdominal wall. The latter depends on the trophism of abdominal muscles, gender, and the curarization of the patient during the procedure.

A third main point to be scrutinized is the long-term platinum retention in body tissues of patients previously treated with systemic chemotherapy [10]. As the HORSE trial has targeted patients with recurrent epithelial ovarian cancer, these patients certainly have received some platinum-based systemic treatment(s) before the SCR plus HIPEC. In other words, the authors should have planned to take peritoneal biopsies just before starting HIPEC (i.e., time point T0) with the purpose of avoiding the potential confounding bias related to the possibility of different cumulative doses of platins at the baseline between treatment groups (i.e., O-SCS vs. MI-SCS). For example, in the Milan's clinical trial (NCT0294979) exploring the effect of high IAP during the closed technique HIPEC in patients with peritoneal metastasis from colorectal carcinoma and *pseudomyxoma peritonei* [3], the residual dose of platins in patients previously treated with the systemic FOLFOX regimen was subtracted from CDDP tissue concentration determined in neoplastic and normal tissues after the HIPEC.

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Another last finding of note is the choice to perform O-SCS vs. MI-SCS was based either on site and extension (isolated or localized vs. peritoneal carcinomatosis) of disease at relapse and thus, the patients selected to MI-SCS trend to have less disease burden than O-SCS group. Despite the authors did not focus this current report on survival outcomes, the trend of improved PFS favoring the MI-SCS may be biased by this factor, which should be taken into account at the time of the final report of this trial.

In conclusion, the initial scientific assumption by Petrillo et al. [1] is sound but the authors did not clearly state it. High IAP induced by pneumoperitoneum could influence the permeability of peritoneal surface and consequently the accumulation of CDDP, by modifying the patency of lymphatic stomata. However, the study is severely flawed by methodological bias. Two fundamental confounders, i.e. IAP and tissue platinum accumulation after systemic chemotherapy (CDDP tissue T0 concentration), were not systematically controlled. The last point of criticism is the interpretation of the data. Differences in CDDP tissue uptake, should they have actually occurred, are likely to be related to eventual differences in IAP that the patients were submitted during the surgical and HIPEC phases of the treatment, and not to the MI approach itself.

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