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The Authors' Reply

We read with interest the comments of Hans Ehrsson about our recent article on the population pharmacokinetics of cisplatin after peroperative intraperitoneal administration.[1] He questions the dose recommendation in view of the relation between cisplatin binding to proteins and the risk of renal toxicity. He argues that, following the dose recommendation described in our paper (higher doses when protein concentrations are lower), the concentration of ultrafiltered fraction of platinum will increase and therefore so will the toxicity. Finally, he has questioned the fact that body surface area was not a significant co-variate on the clearance of total platinum.

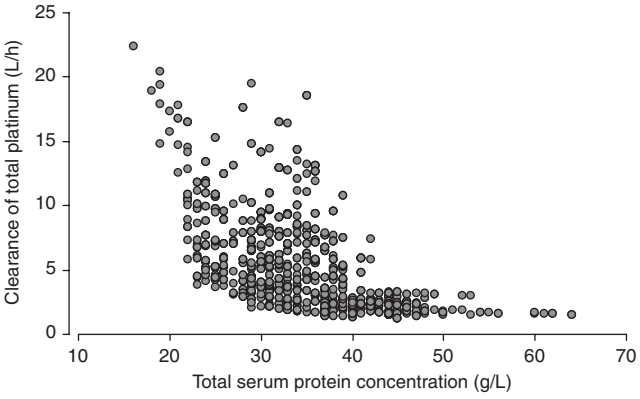

Fig. 1. Relation between clearance of total platinum from the central compartment and observed serum protein concentrations.

We firstly think that the dose recommendation described in the paper does not contradict the fact that the ultrafiltered fraction might be linked to the toxicity of platinum. Indeed, the relation between the clearance of total platinum and serum protein described in the paper clearly shows that the elimination of platinum is higher when protein concentrations are low (figure 1). This is especially the case at the beginning of the chemotherapy, when the protein concentration is lowest.[2] Thus, to maintain sufficient intraperitoneal exposition when protein concentrations are low, one should increase the dose administered, taking into account a given threshold of toxicity. Moreover, as total platinum is the source of ultrafiltered platinum, one can reasonably think that this fraction is also decreased even if its formation is increased when the protein concentration is low.

Secondly, the dose recommendation was built using previously used parameters, not physiopathological parameters, with the aim to optimize both efficacy and toxicity. The parameter of toxicity was the area under the plasma concentration-time curve (AUC) of total platinum, as previously described.[2] We previously compared the AUC of both total and ultrafiltered platinum with regard to toxicity and found that the AUC of total platinum was more relevant. The same conclusion was drawn with a greater number of patients (unpublished data). This confirms the rationale of the dose recommendation building, which was performed using known parameters but not physiopathological parameters for which we have no precise data.

Finally, the fact that body surface area was not observed as a significant co-variate on clearance and the clinical relevance of this co-variate were discussed in our article. It should,

however, be kept in mind that these patients had very low serum protein concentrations and underwent major surgery. Consequently, we think that it is difficult to transpose the co-variates obtained in more regular conditions. In particular, the co-variates obtained in our study might be more relevant in this special context and thus decrease the weak influence of body surface area on clearance of ultrafiltered platinum.

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