Treatment of Ovarian Cancer with Intraperitoneal Platinum: Heating Up the Debate

Emiel A. De Jaeghere, M.D.^{1,*}; Félix B. Gremonprez, M.D., Ph.D.¹; Philippe G. Tummers, M.D., Ph.D.²; Wouter C. Willaert, M.D., Ph.D.³; Wim P. Ceelen, M.D., Ph.D.³; Frédéric C. Amant, M.D., Ph.D.⁴; and Hannelore G. Denys, M.D., Ph.D.¹

¹Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium

²Department of Gynecology, Ghent University Hospital, Ghent, Belgium

³Department of Experimental Surgery, Ghent University Hospital, Ghent, Belgium

⁴Department of Gynecologic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

*Corresponding author: Emiel A. De Jaeghere, Ghent University Hospital, Corneel Heymanslaan 10, B-9000 Ghent, Belgium. Phone: +32 9 332 06 75; Email:

emiel.dejaeghere@ugent.be

Details about competing interests are provided separately (ICMJE Forms and subheading “Declaration of interests”).

Running title: Ovarian Cancer and Intraperitoneal Platinum

In their recent article in *Journal of Clinical Oncology*, Walker et al. reported the efficacy and toxicity profile of bevacizumab with intravenous (i.v.) vs. intraperitoneal (i.p.) chemotherapy for newly diagnosed advanced ovarian cancer in a large intergroup phase 3 trial (GOG-252).¹ Although we appreciate their findings, we believe that the interpretation of the results raises a few important issues for the authors to clarify.

First, GOG-252 confirms that, for advanced ovarian cancer patients, complete macroscopic debulking represents their best chance of long-term survival. It is a deep-rooted belief among the medical community that when ovarian cancer patients are treated by gynecologic oncologists in specialized centers where advanced surgical strategies are performed, both resection rate and prognosis are demonstrably improved.² Given the large number of centers (n=213) and the relatively long accrual time period (28 months) needed to conduct GOG-252, it is unclear whether participant centers were high-volume institutions with expertise in gynecologic oncology. Can the authors comment if institutional patient accrual volume was associated with survival and/or completeness of debulking (e.g., accrual per year per site, forest plot for survival per site, and complete resection rate per site)? For a better understanding of this issue, more detailed information on surgical procedure characteristics would be appreciated (e.g., bowel/diaphragm/spleen resection, blood loss, duration of surgery, surgical complications, and time between surgery and start of adjuvant therapy).

Second, some adverse events were discussed by the authors, but little to no information is available on renal dysfunction and catheter-related events, both of which posed a problem in GOG-172.³ Therefore, we would suggest that the authors report in more detail the observed toxicity rates in this trial.

Third, it is our premise that ovarian cancer, particularly stage IV, is a systemic disease, and systemic chemotherapy—of which platinum remains to this day the unquestioned backbone—should be offered to these women. It is, in fact, the very purpose of i.p. administration to minimize systemic exposure and associated toxicity.⁴ As such, the failure to offer i.v. platinum therapy to stage IV participants in two of three arms when there is substantial data to support its use is,⁵ in our opinion, a serious therapeutic omission—a first in a large phase 3 trial for front-line ovarian cancer. The exploratory data by Walker et al. argue strongly in favor of a therapeutic benefit for i.v. over i.p. platinum in suboptimally resected stage III and stage IV patients since a clinically relevant difference in median overall survival could be observed (55.5 vs. 50.5 vs. 43.6 months for i.v. carboplatin, i.p. carboplatin, and i.p. cisplatin, respectively; n=178).¹ We claim that stage IV patients should never have been included in the trial in the first place. Nevertheless, we would like to know if there actually was a difference in survival between those who received i.v. platinum (n=24) and those who received i.p. platinum (n=68) in this subgroup with stage IV disease specifically?

Until GOG-252, three large intergroup phase III studies have demonstrated the favorable impact of i.p. over i.v. administration of chemotherapy following debulking surgery,^{3,6,7} although differences in dose intensity and schedule of administration between arms confounded interpretation of the i.p. approach. However, we are doubtful if the resoundingly negative GOG-252 trial will be enough to solve this 3-decade oncological conundrum. Until more data is available, it is reasonable to conclude that the most convincing evidence to date for i.p. drug delivery was provided by van Driel and colleagues.⁸ Besides the addition of hyperthermia, major differences with the present

GOG-252 trial are the timing of surgery (interval vs. upfront debulking) and the timing of chemo-instillation (intraoperatively vs. postoperatively). Because i.p. chemotherapy was administered postoperatively in GOG-252, we may assume that the formation of peritoneal adhesions blocked free flow, and thus, uniform access of the chemotherapy into the peritoneal cavity.⁹

In conclusion, GOG-252 proves the large-scale feasibility of i.p. therapy in the adjuvant treatment of ovarian cancer. However, the trial also demonstrates that while i.p. platinum-based therapy has a similar efficacy to current i.v. treatment protocols, it requires more interventions (e.g., catheter placement/removal), is somewhat less tolerable for the patient, and does not result in less systemic toxicity. Additionally, these results are yet another argument in favor of centralized expert referral for ovarian cancer surgery. Finally, we would argue that further research on i.p. therapy in ovarian cancer should focus first on the addition of novel i.p. treatments (e.g., immunotherapy, antibody-drug conjugates, or prolonged delivery platforms) to the standard of i.v. platinum-based therapy, rather than its replacement.

Contributors' statement

All authors contributed substantially to the conception and design of the “Correspondence”. E.A.D. drafted the manuscript and all authors contributed to its final revision. All authors approved the final version of the manuscript for publication.

Declaration of interests

The authors have no conflicts of interest to declare.

Acknowledgements

E.A.D. is an “*Aspirant*” (Ph.D. Fellow) of the Research Foundation-Flanders (*FWO*).

References

1. Walker JL, Brady MF, Wenzel L, et al: Randomized Trial of Intravenous Versus Intraperitoneal Chemotherapy Plus Bevacizumab in Advanced Ovarian Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study. *J Clin Oncol* 10.1200/JCO.18.01568
2. Harter P, Muallem ZM, Buhrmann C, et al: Impact of a structured quality management program on surgical outcome in primary advanced ovarian cancer. *Gynecol Oncol* 121:615-9, 2011
3. Armstrong DK, Bundy B, Wenzel L, et al: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 354:34-43, 2006
4. Carlier C, Mathys A, De Jaeghere E, et al: Tumour tissue transport after intraperitoneal anticancer drug delivery. *Int J Hyperther* 33:534-542, 2017
5. Jayson GC, Kohn EC, Kitchener HC, et al: Ovarian cancer. *Lancet* 384:1376-88, 2014
6. Alberts DS, Liu PY, Hannigan EV, et al: Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 335:1950-5, 1996
7. Markman M, Bundy BN, Alberts DS, et al: Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 19:1001-7, 2001
8. van Driel WJ, Koole SN, Sikorska K, et al: Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *N Engl J Med* 378:230-240, 2018

9. Ceelen WP, Bracke ME: Peritoneal minimal residual disease in colorectal cancer: mechanisms, prevention, and treatment. *Lancet Oncol* 10:72-9, 2009