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Controversies in Oncology: Gynecologic Oncology

Cytoreductive Surgery Plus Platinum-Based Hyperthermic Intraperitoneal Chemotherapy in Epithelial Ovarian Cancer: A Promising Integrated Approach to Improve Locoregional Control

Marco Petrillo,[a] Luigi Pedone Anchora,[a] Giovanni Scambia,[a] Anna Fagotti[a,b]

[a]Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, Italy; [b]Department of Surgery, Division of Minimally Invasive Gynecology, University of Perugia, Perugia, Italy

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Epithelial ovarian cancer (EOC) remains the most lethal among gynecological malignancies, and it is currently estimated as the fifth cause of cancer death in the female population [1]. One of the main reasons related to its unfavorable prognosis is the high rate of peritoneal relapse [2, 3], which strongly emphasizes the need to develop more effective treatments able to increase locoregional control.

In this context, the complete surgical removal of all visible lesions is certainly the cornerstone to adequately treat diffuse peritoneal disease [4]. To this purpose, more complex and comprehensive surgical procedures have been introduced in routine clinical practice to increase the rate of complete cytoreduction, both at initial diagnosis [5] and at the time of relapse [6, 7]. However, even if surgery allows the removal of macroscopic lesions from almost all anatomic sites, microscopic disease cannot be effectively treated by surgery, thus requiring adjuvant approaches to achieve an adequate control.

Focusing on this issue, the intravenous route of administration for adjuvant platinum-based chemotherapy in EOC patients is commonly used by a consistent group of gynecologic oncologists because it provides the best balance between efficacy and safety, when compared with the intraperitoneal (i.p.) route of administration [8]. However, the long-term results of two pivotal randomized clinical trials (Gynecologic Oncology Group [GOG]-114 and GOG-172) reported a median overall survival of 61.8 months in the i.p. arm, which is almost 10 months longer when compared with overall survival of EOC patients receiving standard intravenous treatments [9]. Therefore, even if cisplatin i.p. administration at the time of complete cytoreductive surgery represents just a single infusion, it appears to be an intriguing strategy to potentially exploit some of the benefit of the i.p. route, while minimizing side effects.

In this context, as a further step to improve locoregional control, hyperthermia has been progressively introduced into platinum-based i.p. chemotherapy to increase the efficacy of this class of compounds [10]. In fact, several in vitro and in vivo experimental studies have demonstrated a hyperthermia-related enhancement of cytotoxic properties for several anticancer drugs, including platinum compounds [11]. In particular, the magnitude of hyperthermic sensitization is estimated by using as index the ratio between the tumor cell growth with the drug alone and with the same drug at elevated temperature (thermal enhancement ratio [TER]). Interestingly, at a temperature of 41.5°C, the TER for cisplatin is 1.48, which implies a 50% increase of platinum efficacy using hyperthermic sensitization [12].

Together, the above-cited evidence strongly suggests that the administration of platinum-based hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery may represent an effective strategy to adequately treat both visible and microscopic disease, thus improving locoregional control.

Furthermore, besides this strong rationale, other clinical considerations may support the use of HIPEC after cytoreductive surgery in patients with EOC. In particular, two European cooperative groups (Arbeitsgemeinschaft Gynäkologische Onkologie [AGO-OVAR] and Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens [GINECO]) recently reviewed the results of three randomized clinical trials, which enrolled a very large population of 3,388 newly diagnosed EOC patients [13]. Interestingly, the authors demonstrated that a delayed start of chemotherapy is associated with earlier disease recurrence and decreased overall survival in patients with no residual tumor after surgery. Moreover, the authors estimated an 8.7% increase of mortality for every 7 days of chemotherapy delay in the group of patients submitted to complete surgical debulking. These findings appear much more relevant, considering that, to achieve the surgical goal of no gross residual disease, a very challenging surgery is often required with long recovery time and increased chemotherapy delay [13]. It could be argued that the addition of HIPEC may increase toxicities and delay postoperative therapy, but there is no evidence of a longer time to chemotherapy in patients receiving cytoreductive surgery plus HIPEC [14, 15]. Therefore, particularly when complete surgical debulking is achieved, the administration of platinum-based HIPEC after surgery seems to represent the best strategy to immediately start adjuvant chemotherapy, thus potentially improving locoregional control, and prognosis.

Considering this solid rationale, several efforts have been made to test the safety of HIPEC in EOC patients. However, because of the lack of randomized clinical trials, controversies exist in the scientific community regarding the potential risk of increased morbidities

Correspondence: Anna Fagotti, M.D., Ph.D., Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Largo A. Gemelli, 8, 00168 Rome, Italy. Telephone: 390630154979; E-Mail: annafagotti@libero.it Received December 9, 2015; accepted for publication February 4, 2016; published Online First on March 23, 2016. 1083-7159/2016/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2015-0500

related to the use of HIPEC after debulking surgery [16]. For instance, it is difficult to estimate specific HIPEC-related toxicities because this strategy is usually performed after complete surgical debulking, which obviously carries on morbidities in accordance with the complexity of surgery. Furthermore, across the literature, HIPEC has been used in several clinical settings, such as women with platinum-resistant disease, and employing nonplatinum compounds (mytomicin, anthracyclines, and taxanes), which can provide additional toxicities without clinical benefits. However, if we look at the experiences using platinum compounds, we did not observe increased HIPEC-related postoperative morbidities. In fact, the rate of complications after cytoreductive surgery without HIPEC ranges from 20% to 30%, as reported in retrospective series [17] and prospective clinical trials [18]. At the same time, the revision of the literature regarding the addition of HIPEC to cytoreductive surgery documents a rate of postoperative morbidities ranging from 15% to 35%, which is superimposable to data reported for cytoreductive surgery alone [16, 19–24]. As a further confirmation of the safety of cisplatin-based HIPEC, two recently published phase I studies have clearly demonstrated that cytoreductive surgery followed by HIPEC does not affect the chance of administering conventional intravenous adjuvant chemotherapy [14, 15]. Furthermore, the analysis of the pharmacokinetic profile showed that when cisplatin is administered intraperitoneally in the context of HIPEC, high drug concentrations in peritoneal tissue are achieved with a very low systemic exposure [14, 15]. However, these data provide only an initial level of evidence supporting the safety of cytoreductive surgery plus HIPEC; therefore, only a comparison between homogeneous groups of patients will definitively answer this question. In this context, as recently presented at the 2015 Society of Gynecologic Oncology Annual Meeting, the preliminary analysis of the HIPEC Ovarian Cancer Recurrence (HORSE) trial (ClinicalTrials.gov identifier NCT01539785) showed no differences in terms of moderate/severe postoperative complications (Memorial Sloan Kettering Cancer Center grading system) and quality of life (QoL) measures [25] between platinum-sensitive recurrent EOC patients randomly assigned to receive secondary cytoreductive surgery (SCS) alone or SCS plus HIPEC. These encouraging preliminary safety and QoL data reported in the HORSE trial are also supported by a recently published French retrospective analysis on a large cohort of 216 ovarian cancer patients [26]. Therefore, data from several retrospective series [19–24], phase I clinical trials [14, 15], and preliminary analysis of phase III randomized clinical trials [25] confirm that the administration of HIPEC in the context of cytoreductive surgery is a safe procedure in women with ovarian cancer.

Despite these encouraging findings regarding safety, as for every novel therapeutic approach, a proven benefit in terms of prolongation of survival is mandatory for its introduction into routine clinical practice. Levels of evidence supporting the use of HIPEC in EOC are currently low (II-2 according to Canadian Task Force classification), and we need to wait for mature survival data from phase III randomized clinical trials to draw any definitive conclusions on this topic. However, even if not conclusive, the available evidence, coming from case-control studies, appears to be very encouraging and strongly suggests the active investigation of the role of this treatment strategy in EOC [27–31].

In our case-control study published a few years ago, we observed a longer 2-year (HIPEC group = 96.7% vs. no HIPEC group = 75.7%; $p = .017$) and 5-year (HIPEC group = 68.4% vs. no HIPEC group = 42.7%; $p = .017$) overall survival in platinum-sensitive recurrent EOC patients receiving SCS plus HIPEC, compared with women treated with chemotherapy alone or SCS plus chemotherapy [28]. However, the most interesting finding from our experience was the observation of a longer secondary platinum-free interval (PFI) compared with primary PFI in 53.4% of women with recurrent disease receiving SCS plus platinum-based HIPEC [28]. Interestingly, these data have been also confirmed by several French groups in large cohorts of recurrent ovarian cancer patients [24, 32]. It could be argued that the longer secondary PFI compared with primary PFI is the result of a selection bias, but even in this case the presence of accumulating favorable evidence from several different Institutions strongly suggests that a rationale exists to test the efficacy of HIPEC in specific settings of ovarian cancer patients.

Furthermore, survival data regarding the use of HIPEC in platinum-sensitive recurrent ovarian cancer appear attractive when considered in the context of the available literature. In fact, the progression-free survival reported in women with platinum-sensitive disease receiving platinum-based chemotherapy plus target-based agents (olaparib, bevacizumab) is approximately 12 months [33, 34], which appears significantly lower compared with the progression-free survival reported in patients treated with SCS plus HIPEC (24 months) and adjuvant chemotherapy with standard carboplatin/paclitaxel only [28]. Survival data regarding the use of SCS plus HIPEC are also encouraging when compared with the outcome of women treated with SCS alone. In particular, we recently reported in a long-term survival analysis a median postrelapse survival of approximately 60 months [35], which is very favorable when compared with data from prospective studies [18] investigating the role of SCS without HIPEC in platinum-sensitive recurrent ovarian cancer (50 months).

Obviously, the above-presented comparisons, as others have recently reported [16], are not very reliable, because HIPEC patients are carefully selected, and all are treated with a complete debulking. However, we may state that SCS+HIPEC is at least not inferior to other therapeutic options, thus supporting to continue the on-going investigations. Furthermore, data supporting the efficacy of HIPEC are progressively extending from platinum-sensitive recurrent disease to patients with platinum-resistant and newly diagnosed advanced ovarian cancer [24, 32]. In particular, the increased drug levels in the peritoneum may potentially reverse platinum resistance, thus justifying the favorable results recently reported by the French groups [24, 32]; however, caution should be taken before attempting SCS plus HIPEC in platinum-resistant recurrences, considering the very limited evidence supporting surgery in this specific clinical setting [36, 37].

Finally, in a recent critical appraisal [16], it was hypothesized that, as reported in colorectal cancer [38], a disappearance of the HIPEC-related survival benefits might be possible with a long-term follow-up. In this context, the results of our recently published 7-year analysis demonstrating a very favorable postrelapse survival of approximately 60 months does not support such a hypothesis [35], and our data also appear reasonable considering the relevant differences between ovarian and colorectal cancer in terms of sensitivity to cytotoxic agents.

In conclusion, because ovarian cancer remains the biggest challenge for gynecologic oncologists, it is important for the scientific community to actively investigate and fully exploit every novel promising therapeutic strategy. The addition of HIPEC to cytoreductive surgery is supported by a solid biological and clinical

rationale, with preliminarily encouraging safety and survival data, particularly in patients with platinum-sensitive recurrent disease. The rigorous analysis of the results from ongoing phase III randomized clinical trials will clarify in the future whether, and how, this therapeutic approach should be introduced into routine clinical practice.

Author Contributions

Conception/Design: Marco Petrillo, Anna Fagotti

Provision of study materials or patients: Giovanni Scambia, Anna Fagotti

Collection and/or assembly of data: Marco Petrillo, Luigi Pedone Anchora

Data analysis and interpretation: Marco Petrillo, Luigi Pedone Anchora, Giovanni Scambia, Anna Fagotti

Manuscript writing: Marco Petrillo, Luigi Pedone Anchora, Giovanni Scambia, Anna Fagotti

Final approval of manuscript: Marco Petrillo, Luigi Pedone Anchora, Giovanni Scambia, Anna Fagotti

Disclosures

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