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Review

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Management of Advanced Ovarian Cancer. A Literature Review

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Abstract

The rationale behind the use of hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery is the association between pharmacological activity of chemotherapy delivered to the peritoneal cavity with the enhanced cytotoxic effect of hyperthermia. Data on the efficacy of HIPEC in the primary debulking surgery (PDS) setting are still controversial and limited by the small sample size of most of the studies, the inclusion of different treatment settings and chemotherapy regimens. Among the ongoing prospective trials, only the OVHIPEC-2 trial is investigating exclusively patients submitted to PDS ± HIPEC with cisplatin 100 mg/m^2 and results are expected by 2026. On the interval debulking surgery (IDS) setting high quality data are coming from the result of the OVHIPEC-1 trial, which demonstrated a survival advantage of nearly 4 months in median progression-free survival (PFS) (14.2 months *vs*. 10.7 months; $p = 0.003$) and almost 12 months in median overall survival (OS) (45.7 months *vs*. 33.9 months; $p = 0.02$) for HIPEC treated patients (cisplatin 100 mg/m^2) compared to no-HIPEC group, with comparable morbidity. However, due to some criticisms raised to the results of OVHIPEC-1 trial, the ESMO-ESGO guidelines recommended not to consider HIPEC as standard therapy until results from ongoing randomized control trials (RCTs) are provided. On the contrary, for the National Comprehensive cancer network (NCCN) guidelines HIPEC can be considered at the time of IDS. Similarly, data supporting the role of HIPEC in association with surgery in case of recurrent disease appear to be controversial in terms of patients and selection and intraperitoneal chemotherapy regimen. Indeed, despite the positive results coming from a prospective randomized trial, they appear to be biased by the inclusion of both platinum sensitive and resistant disease and the lack of information on PFS. Those results are in contrast with data coming from another prospective trial, which failed to demonstrate a survival gain of recurrent ovarian cancer patients treated with secondary cytoreductive surgery + HIPEC with carboplatin (800 mg/m^2 for 90 min) compared to women submitted to cytoreduction only. Again, in this subgroup of patients data of ongoing RCTs are awaited to assess the impact on survival of HIPEC administration in case of recurrent disease.

Keywords: ovarian cancer; HIPEC; primary debulking surgery; interval debulking surgery; recurrent disease

1. Introduction

Ovarian cancer is the most lethal among all gynecological malignancies, ranking the eighth in both incidence and mortality in women's cancers [1] with 75% of patients diagnosed with an advanced stage disease [2]. In presence of peritoneal carcinomatosis, the role of primary cytoreductive surgery to no gross residual disease (NGR) followed by platinum-based adjuvant chemotherapy has been widely demonstrated to significantly improve patient's prognosis [3–5].

Due to the typical spreading pattern of the disease, the option of delivering chemotherapy agents directly to peritoneal cavity in addition to standard treatment has been investigated over the past decade [6]. Also, the addition of hyperthermia to intraperitoneal drug delivery has shown to increase the cytotoxic effect of chemotherapy, further enabling this treatment to target microscopic tumor deposits inside peritoneal cavity [7].

Despite available data on this topic appear to be heterogeneous in terms of timing of therapy delivery and choice of chemotherapy agents, high quality data coming from a recent phase-III trial [8] are supporting the positive effect of hyperthermic intraperitoneal chemotherapy (HIPEC) in prolonging patient's survival.

On this background, with this manuscript we provide a comprehensive review of available data on HIPEC administration and efficacy in advanced ovarian cancer patients.

2. Why Hyperthermic?

Overall, the rationale behind the use of HIPEC after cytoreductive surgery is the association between pharmacological activity of chemotherapy directly delivered to the peritoneal cavity, with the enhanced cytotoxic effect of hyperthermia [6].

Historically, this latter aspect was firstly described by Conley [9] in 1893, who noticed a spontaneous tumor regression in patients with high body temperature due to erysipela inoculation.

Indeed, hyperthermia appeared to be able to cause tumor cells necrosis due to cytoplasmatic swelling, direct nu-

cleus and DNA damage and disruption of cell membrane [10].

In addition, it was further demonstrated that tumor cells are more sensitive to hyperthermia with respect to normal cells and that different tumors are sensitive to specific temperatures [11,12].

After that and for many decades, the effect of hyperthermia was studied in association with various cancer treatment strategies such as chemotherapy and radiotherapy, with promising results [13,14].

In epithelial ovarian cancer, the mechanism according to which hyperthermia is able to cause tumor damage seems to be multifactorial. Firstly, causing vasodilation, high temperature appears to increase cancer cells exposure to chemotherapy agents, thus overcoming potential chemotherapy resistance due to dysfunctional microcirculation [15].

Secondly, the vasodilation and subsequent improved perfusion, appear to increase the concentration of immune cells at tumor site and promote their adhesion to cancer cells [15].

Thirdly, there is evidence that hyperthermia can interfere with DNA repair mechanisms and therefore obstruct cancer treatment resistance [16].

Ultimately, hyperthermia can facilitate chemotherapy intracellular uptake and therefore positively enhance treatment effect [7].

Since there is no evidence that surgical disruption of plasma-peritoneal barrier has a negative impact on intraperitoneal chemotherapy uptake [7], the potential effect of this treatment in association with various timing of cytoreductive surgery has been widely investigated with promising and heterogeneous results.

3. HIPEC in Primary Debulking Surgery

Currently, data on HIPEC at the time of primary debulking surgery (PDS) are overall lacking.

Indeed, available data on safety and feasibility of HIPEC at the time of PDS are mainly limited by the inclusion of different treatment settings and chemotherapy regimens and by an overall small sample size.

Despite the above-mentioned limitations, the only study providing survival results on this topic is a still unpublished prospective phase II trial presented at American Society of Clinical Oncology (ASCO) meeting in 2017 by Lim *et al*. [17]. This trial failed to demonstrate a survival advantage in patients treated with HIPEC compared to patients submitted to cytoreduction only, despite a comparable morbidity. Indeed, out of 184 patients, the 5-year progression-free survival (PFS) was 20.9% and 16.0% in HIPEC and non-HIPEC group respectively ($p = 0.569$) and 5-year overall survival (OS) was 51.0% and 49.4% respectively ($p = 0.574$). However, this study included a 69% of patients who received neo-adjuvant chemotherapy (NACT) due to higher disease distribution, therefore, despite not significant and deserving further evaluation, these data show an increasing trend towards better survival in HIPEC group.

In terms of reproducibility of HIPEC treatment in this subset of patients, positive results were achieved by Paris *et al*. [18] in a phase II monocentric single arm study, who however reported a lower rate of post-operative G3 and G4 complications (12.5% and 7.5%, respectively) among 40 patients submitted to HIPEC with carboplatinum and paclitaxel at the time of PDS, subsequently treated with Bevacizumab as a maintenance therapy (82.5% of the included population).

On this background, some prospective randomized trials have been designed and are currently ongoing in order to overcome existing issues on this subject and provide additional survival results.

Among them, the multicentric international OVHIPEC-2 trial [19] is planning to enroll 538 International Federation of Gynecology and Obstetrics (FIGO) [20] stage III ovarian cancer patients undergoing PDS to <2.5 mm residual disease to randomly receive or not receive HIPEC with cisplatinum 100 mg/m^2, followed by standard adjuvant chemotherapy with carboplatinum and paclitaxel. Survival results and data on morbidity are expected by 2026.

Parallel to that, similar endpoints are present in the HIPEC-04 [21], a prospective randomized trial which is currently recruiting newly diagnosed ovarian cancer patients undergoing cytoreductive surgery $\pm$ HIPEC with with Docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 intraperitoneally in succession. Alongside with that, results of the CHORINE TRIAL [22], a randomized control study investigating the use of HIPEC with cisplatin + paclitaxel in the upfront setting, are expected in the near future.

The results of the above-mentioned trials are awaited to help assess safety and oncological outcomes of HIPEC in the upfront setting for advanced ovarian cancer patients.

4. HIPEC in Interval Debulking Surgery

Before November 2018, data on the use of HIPEC in the interval cytoreductive setting suffered from the same limitations described for patients undergoing upfront surgery, being available evidence overall scarce, mainly retrospective and carried out in very heterogeneous patient populations (primary, recurrence) [23].

So far, the largest high-quality evidence supporting the use of HIPEC exclusively in patients candidate to NACT followed by interval debulking surgery (IDS) are coming from the results of a prospective randomized trial (OVHIPEC-1) published by Van Driel *et al.* [24].

Indeed, the OVHIPEC-1 trial [24] enrolled 245 FIGO stage [22] III ovarian cancer patients undergoing IDS, randomly assigning them to receive or not receive HIPEC with cisplatin100 mg/m^2 in case of Residual tumor (RT) <2.5 mm at the end of the cytoreductive procedure.

Interestingly, survival analysis showed a gain of nearly 4 months in median PFS (14.2 months *vs*. 10.7 months; $p = 0.003$) and almost 12 months in median OS (45.7 months *vs*. 33.9 months; $p = 0.02$) for HIPEC treated patients compared to no HIPEC group.

Also, for the analyzed populations the time of chemotherapy re-initiation was comparable in the two groups (30 days in the surgery group and 33 days in the surgery-plus-HIPEC group), as well as adverse events rate/toxicity profile which appeared not to be affected by HIPEC administration ($p = 0.760$). As a matter of fact, HIPEC toxicity has been a major concern since the IP administration of chemotherapy agents started to become a promising option in advanced ovarian cancer patients, being acute renal failure the most common adverse event. However, this side effect appeared to be preventable by the infusion of Sodium Tiosulphate in case of Cisplatin IP administration [25], as demonstrated in the OVHIPEC-1 trial [24].

On this setting, the feasibility of HIPEC at the time of IDS was further confirmed by another prospective study [26], which also reported similar rate of intra-operative and post-operative complications ($p = 0.189$ and $p = 0.238$; respectively) in the group of patients receiving HIPEC with cisplatin 100 mg/m^2 compared to women non submitted to the treatment. In addition to that and in contrast with OVHIPEC-1 results [24], no difference in bowel diversion rate between the two groups was observed ($p = 0.213$), meaning that HIPEC should probably no longer be considered as a risk factor for anastomotic leak [26].

Also, among patients enrolled in Van Driel's trial [24] HIPEC administration didn't affect neither patient's quality of life [27], nor the economic burden on health-care providers [28].

Those results have been supported by a very recently published prospective Phase II trial [29], which analyzed 70 IDS patients, 50% of them randomized to receive HIPEC with cisplatin 75 mg/m^2. The results confirmed an improved PFS (primary endpoint of the study) in the HIPEC treated patients (18 months in experimental group *vs* 12 months in the control group; $p = 0.038$) with comparable morbidity ($p > 0.05$) and quality of life evaluation.

Despite being the largest study of prospective nature available on this topic, the results of OVHIPEC-1 trial [24] have been object of controversies between the experts on this field.

The main criticisms raised to the study [24] included the overall small sample size, the long recruitment period, the timing randomization as a possible surgical bias, the imbalance of histology subtypes (despite not statistically significant) and the incorrect reporting of treatment adverse effects [30]. For these reasons, many authors do not agree in including HIPEC in daily clinical practice until more data on its efficacy and safety are provided [30].

The skepticism expressed by some authors on the results of OVHIPEC-1 trial [24] have been reinforced by the fact that its results are in contrast with data provided by Lim *et al*. [17], which did not demonstrate a survival advantage in ovarian cancer patients treated with HIPEC after cytoreductive procedure. However, the authors themselves stated that a longer follow-up is required to confirm the survival outcomes of their study, especially in the group of patients receiving NACT.

Indeed, as previously discussed, their data appear to be weakened by the heterogeneity and the limited numerosity of the included population (both PDS and NACT-IDS treated patients).

Overall, as other large prospective studies are needed to assess whether OVHIPEC-1 [24] results are confirmed, the most recent ESMO-ESGO guidelines [4] recommended not to consider HIPEC as standard therapy and to limit its use to well-designed prospective RCTs [4]. On the contrary, the National Comprehensive cancer network (NCCN) guidelines [31] states that HIPEC can be considered at the time of IDS for FIGO stage III [20] disease.

Currently, other trials are ongoing with the aim to investigate the role of HIPEC in the IDS setting.

The HIPEC-03 trial [32] is a still not recruiting Phase III Multicenter Prospective Randomized Trial. This trial is planning to randomize at least FIGO stage [20] III ovarian cancer patients to receive standard regimen of NACT followed by IDS, or to receive paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 intraperitoneally in succession as neoadjuvant treatment before 2 cycles of standard regimen of neoadjuvant chemotherapy, followed by IDS and HIPEC re-administration at the end of the cytoreductive procedure.

Alongside with that, the CHIPPI trial [33] is currently randomizing advanced ovarian cancer patients to receive or not receive HIPEC with cisplatin 100 mg/m^2 at the end of cytoreductive procedure. Main differences with OVHIPEC-1 [24] trial lay in the inclusion of both upfront surgery and IDS patients and the neoadjuvant chemotherapy regimen which consists in 6 cycles of carboplatin and paclitaxel in both arms.

Indeed, prospective data demonstrate both the feasibility [26] and the favorable oncologic outcomes of HIPEC administration at the time of IDS even after 6 cycles of NACT [34].

Results of the previously mentioned RCTs are awaited to potentially confirm OVHIPEC-1 trial [24] results and overcome highlighted limitations in order to further improve in identifying patients who are the best candidate and may benefit the most from HIPEC administration.

5. HIPEC in Recurrent Disease

The administration of HIPEC in recurrent advanced ovarian cancer and its correlation with patient's survival has been evaluated in few prospective studies.

Evidence from a prospective multicenter observational study published in 2015 by Coccolini *et al*. [35], showed HIPEC with cisplatin + paclitaxel at the time of cytoreductive surgery to be feasible, with a 35% of patients undergoing Grade 3 and Grade 4 post-operative complications according to the Common Terminology Criteria for Adverse Events (CTCAE) scale [36].

However, the results appear to be weakened by the inclusion in this study of 54 patients undergoing surgery in the upfront setting but also for disease recurrence. In addition, both platinum sensitive and resistant diseases were included.

In 2015 Spiliotis *et al*. [37], randomly assigned 120 patients with recurrent disease to receive secondary cytoreductive surgery ± HIPEC, followed by adjuvant chemotherapy in both arms. Survival analysis of this population showed improved overall survival in the group of patients receiving HIPEC compared to women not submitted to that treatment (26.7 months *vs* 13.4 months, respectively; $p = 0.006$).

Despite their promising results, the main limitation of this study consists in the inclusion of recurrent ovarian cancer patients with both platinum sensitive and resistant disease, the latter population accounting for 38% of the entire cohort. Due to that, two different HIPEC protocols were administered in relation to platinum sensitivity of the patient: cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 for platinum sensitive disease, doxorubicin 35 mg/m^2 and paclitaxel 175 mg/m^2 or mitomycin 15 mg/m^2 for platinum resistant disease.

Also, the study did not provide data on PFS, previous chemotherapy regimen was not reported as well as toxicity related to HIPEC administration, if any.

Interestingly, in a subgroup analysis of HIPEC group, mean survival was not different between patients with platinum-resistant disease versus platinum-sensitive disease (26.6 *vs* 26.8 months).

On this topic the positive effect of platinum based-HIPEC in platinum sensitive recurrent ovarian cancer patients has been initially evaluated by Petrillo *et al*. [38] ,who retrospectively analysed data on 70 consecutive patients treated with secondary cytoreductive surgery and HIPEC.

With a median follow-up time of 73 months and a median Platinum free interval of 19 months, 5- and 7-year post-recurrence survival rates were 52.8 and 44.7 for HIPEC and no-HIPEC treated patients, respectively.

More recently, prospective data coming from a phase II randomized trial [39] showed different results, failing to demonstrate a survival gain of recurrent ovarian cancer patients treated with secondary cytoreductive surgery + HIPEC with carboplatin (800 mg/m^2 for 90 min) compared to women submitted to cytoreduction only (52.5 *vs* 59.7 months, respectively; $p = 0.31$). Also, PFS in HIPEC patients was 12.3 months compared to 15.4 months in non-HIPEC patients.

However, this study did not report any difference in intra and post-operative morbidity in terms of oostomy rate, length of stay and treatment related toxicity between the two arms.

Overall, in recurrent ovarian cancer as in other previously discussed treatment settings, available data appear to be controversial in terms of which population may benefit the most from HIPEC administration after surgery (platinum sensive or resistant disease) and which intraperitoneal chemotherapy regimen is preferrable, as carboplatin appear to have a lower synergistc effect with hyperthermia compared to cisplatin [6].

Currently, of the two ongoing trials exclusively focusing on the use of HIPEC in relapsed ovarian cancer one, the HIPOVA-01 trial [40] aims to recruit 132 patients with platinum refractory disease and treat them with surgery + HIPEC with cisplatin 70 mg/m^2 $\times$ 60 min.

Alongside with that, the CHIPOR trial [41] is planning to enroll platinum sensitive recurrent ovarian cancer patients and randomizing them to receive either 6 platinum-based chemotherapy cycles followed by secondary cytoreductive surgery + HIPEC with cisplatin 75 mg/m^2 $\times$ 60 min, or neo-adjuvant chemotherapy and secondary cytoreductive surgery only.

However in this moment both trials appear to be active but still not recruiting. Parallel to that, results on a concluded randomized trials on the use of HIPEC in platinum-sensitive recurrent ovarian cancer are awaited [42].

6. Conclusions

The positive association of hyperthermia to intraperitoneal chemotherapy has been studied in many types of peritoneal cancer [43] so far, not only of gynecological origin.

The interest in HIPEC as a treatment able to prolong ovarian cancer patients' survival is quite novel in the gynecologic oncology literature and it has been raising in the last decade due to encouraging upcoming evidences.

So far, despite not universally accepted, the addition of platinum-based HIPEC only after interval cytoreductive surgery appear to be supported by enough evidence [26,31] to be introduced in daily clinical practice, also in view of its demonstrated not increased morbidity rate compared to standard treatment [28].

Same level of evidence are currently lacking in upfront surgery and recurrent setting, however promising results are awaited from ongoing randomized controlled trials.

Future aspects of interest in this field will be the potential influence of tumor's molecular biomarkers on HIPEC efficacy or the influence of specific patient's genetic patterns on its effectiveness, such as Breast Cancer Gene (*BRCA*) mutation. Also, studies on a potential different recurrence pattern after HIPEC treatment (e.g., potential increased rate of extra-abominal or retroperitoneal relapse [44]) are highly encouraged to further personalize our patients treatment and improve their prognosis.

Author Contributions

VG—Conceptualization, writing original draft, review and editing; RT—Conceptualization, review; EG—Conceptualization, review; GS—Conceptualization, review and editing; AF—Conceptualization, writing original draft, review and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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