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HIPEC in ovarian cancer treatment: current evidence and future perspectives

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ABSTRACT
Despite improvements in surgical and medical treatment, ovarian cancer (OC) remains the most lethal gynecologic malignancy. Clinical evidence has shown promising results for hyperthermic intraperitoneal chemotherapy (HIPEC) during surgery in OC treatment. Recently a phase III randomized clinical trial by van Driel et al. has confirmed the importance of HIPEC during interval debulking surgery improving overall survival and recurrence free survival. The aim was to investigate the rationales for HIPEC in OC treatment, reviewing current scientific literature by analyzing its safety and efficacy. Additionally, the possibility to associate HIPEC with new drugs and targeted therapy was reviewed. In conclusion, the analysis of current data confirmed that HIPEC can improve the outcome of patients with OC representing a valid option to change future clinical practice.

Keywords: ovarian cancer; hyperthermic intraperitoneal chemotherapy (HIPEC); personalized therapy; PARP-Inhibitors, BRCA; immunotherapy; cytoreductive surgery.

SOMMARIO
Il carcinoma ovarico rappresenta la principale causa di morte per tumori ginecologici nei paesi industrializzati, nonostante l'importante evoluzione in ambito medico e chirurgico del suo trattamento. L'evidenza scientifica ha già dimostrato, in passato, l'efficacia della chemioipertermia intraperitoneale al momento della chirurgia (HIPEC) nel trattamento del tumore ovarico; recentemente, lo studio randomizzato di fase III di van Driel et al. ha confermato l'importanza dell'HIPEC al momento della chirurgia di intervallo mostrando un miglioramento in termini di overall survival e di recurrence free survival. Lo scopo di questo articolo è quello di analizzare il razionale dell'utilizzo dell'HIPEC nel trattamento del tumore ovarico, studiandone la sua sicurezza ed efficacia, attraverso un'attenta revisione della letteratura scientifica corrente e di analizzare la possibilità di associare l'HIPEC a nuove terapie mediche come le targeted therapy e l'immunoterapia. La nostra analisi ha dimostrato che l'HIPEC rappresenta una valida opzione nel trattamento del tumore ovarico, migliorando l'outcome delle pazienti affette da tale patologia, in grado di poterne cambiare la future gestione clinica.

INTRODUCTION
Ovarian cancer is the most frequent cause of death for gynecological malignancies in Western countries. The majority of patients are diagnosed at an advanced stage (AEOC), when disease has spread to the peritoneal surface. The gold standard for AEOC treatment is primary debulking surgery (PDS) aiming at macroscopically complete tumor resection followed by intravenous chemotherapy with carboplatin and paclitaxel. For non-eligible patients to undergo PDS three cycles of intravenous neoadjuvant chemotherapy (NACT) are administered followed by interval cytoreductive surgery (IDS)[1,2].

Following the experience in carcinosis of gastrointestinal tumor treatment[3,4], some authors have suggested that hyperthermic intraperitoneal chemotherapy (HIPEC) surgery can improve the prognosis of AEOC patients[5]. The interest about the use of HIPEC in OC has been highlighted by a recent phase III randomized study published by van Driel et al[6] reporting the efficacy of adding HIPEC to IDS in terms of recurrence free survival and overall survival (OS). However, despite some promising results and the attempt to implement

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this procedure to clinical guidelines for OC treatment (AIOM), currently, the consensus on the efficacy of HIPEC is still low. This article summarizes the pros and cons and the future prospects of HIPEC in OC treatment.

RATIONALE FOR HIPEC TREATMENT IN OVARIAN CANCER

The rationale supporting HIPEC in OC treatment is based on the fact that OC is a loco-regional illness with its natural development mainly involving the peritoneal cavity.

From a pharmacological perspective, intraperitoneal (IP) drug administration in peritoneal carcinomatosis is potentially advantageous compared to intravenous therapy. In fact, IP drug delivery increases peritoneal penetration up to 3-5 mm compared to a systemic treatment. Moreover, peritoneal clearance of drugs is significantly slower than the plasmatic clearance, which allows a longer exposure and higher drug concentration to the peritoneal tumor tissue. In addition, IP drug delivery shows effectiveness treating small size peritoneal tumor nodules characterized by pronounced hypoxia and poorly vascularization limiting the efficacy of intravenous drugs[7]. Consistently with these data, several clinical trials demonstrated IP chemotherapy effectiveness in OC treatment, despite feasibility limitations of the procedure[8] as the demand for a multidisciplinary specialized team with expertise, which may be absent in smaller centers and a resource increase in terms of space and time[9]. Furthermore, IP drug administration is known for negative medical implications as abdominal pain, an increased infection risk and potential toxicity caused by the placement of an IP drainage.

The additional use of hyperthermia (HT) to intraperitoneal chemotherapy improves the efficacy of the loco-regional treatment, because HT has several potential antineoplastic properties in its individual application and when combined with different other drugs[10,11]. In fact, HT has been proven to enhance cytotoxicity of platinum compounds[10], to sensitize OC cells lines to cisplatin[12] and to reduce the hypoxic-inducible factor (HIF-1) molecule, a main vascular endothelial growth factor (VEGF) inducer[13]. Moreover, HT increases tumor blood supply and oxygenation of exposed tissues, thus resulting in increased tissue penetration and sensitivity to chemotherapy[14]. Finally, HT improves markedly the anti-tumor immune response stimulating the production and activation of heat shock proteins (HSP) increasing both the innate and the adaptive immune responses to tumors[15].

The potential therapeutic effect, even with a "one shot" IP drug administration under hyperthermic conditions with HIPEC, is supported by the finding that there is a survival benefit in favor of IP regimens even for patients receiving less than 6 cycles of chemotherapy after surgery[16]. Moreover, the use of HIPEC directly during cytoreductive surgery (CRS) allows to overcome the problem of postoperative adhesions formation that can hinder IP drug perfusion. Finally, providing HIPEC during CRS implies an immediate chemotherapy start. This last aspect is particularly favorable for the treatment of OC, because pursuing maximal surgical effort is associated with improved survival, but usually carries an unavoidable time to chemotherapy (TTC) delay, which can in consequence increase mortality. Estimates suggest, a delay in chemotherapy treatment by 7 days results in 8.7% mortality increase in patients with complete surgical debulking[17].

Therefore, chemotherapy during surgery seems to be the most time efficient procedure to introduce the benefit of IP drug delivery without related postoperative toxicities in OC.

CLINICAL DATA WITH HIPEC IN OC

Despite the fact that HIPEC has been introduced in OC care more than 20 year ago, available data are largely inconclusive. Reviewing scientific literature, study designs demonstrate often several weaknesses, such as small sample size, very heterogeneous clinical settings including primary, recurrent and persistent disease plus numerous chemotherapy approaches with different dosages and time of perfusion, complicating the comparison of data and leading to a low evidence level to support the importance of HIPEC in OC.

A systematic review by Zivanovic et al[18] including 12 retrospective studies, suggests patients treated with HIPEC have an increased progression-free survival (PFS) and overall survival (OS) with an acceptable rate of complications and 30-day mortality.

Several case-control studies suggest an improvement of PFS and OS in patients submitted to HIPEC both at first diagnosis and at time of recurrence (**Table. 1, 2 and 3**)[19,20].

Table 1
Case control studies in recurrent ovarian cancer

Study	Period of enrollment	No. of pts with HIPEC	No. of pts without HIPEC	Criteria of optimal cytoreduction before HIPEC in subgroup analyses	**PSF**	**OS**
Munoz-Casares et al. 2009[34]	1997-2004	14	12	RT ≤ 1 cm	↑	↑
Fagotti et al. 2012[35]	2005-2009	30	37	RT ≤ 1 cm	↑	↑
Safra et al. 2014[36]	Not mentioned	27	84	No visible tumor RT ≤ 1 cm	↑	↑
Le Brun et al. 2014[37]	1997-2011	23	19	No visible tumor RT ≤ 1 cm	n.a.	↑
Cascales-Campos et al. 2015[38]	2001-2012	32	22	No visible tumor RT ≤ 1 cm	↑	n.a.
Marocco et al. 2016[39]	1995-2012	19	27	No visible tumor RT ≤ 1 cm	=/↑	↑
Baiocchi et al. 2016[40]	2000-2014	29	50	Not performed	=	=

Table 2
Case control studies in upfront ovarian cancer

Study	Period of enrollment	No. of pts with HIPEC	No. of pts without HIPEC	Criteria of optimal cytoreduction before HIPEC in subgroup analyses	**PSF**	**OS**
Ryu et al. 2004 41	1994-2000	57	60	RT ≤ 1 cm	↑	↑
Gori et al. 2005 42	1991-1997	29	19	No visible tumor RT ≤ 1 cm	n.a.	↑
Kim et al. 2010 43	1991-2004	19	24	No visible tumor RT ≤ 1 cm	n.a.	↑
Cascales-Campos et al. 2014 44	1998-2011	52	35	No visible tumor RT ≤ 1 cm	↑	n.a.
Mendivil et al. 2017 45	2012-2015	69	69	No visible tumor RT ≤ 1 cm	↑	=

Table 3
Randomized Clinical Trials about HIPEC in ovarian cancer

Study	Period of enrollment	Disease Status	No. of pts with HIPEC	No. of pts without HIPEC	Criteria of optimal cytoreduction before HIPEC in subgroup analyses	**PSF**	**OS**
Spiliotis et al. 2015[21]	2013-2016	Recurrent	60	60	Not performed	n.a.	↑
Van Driel et al. 2018[6]	2007-2016	First Diagnosis	122	123	Not performed	↑	↑

However, only two randomized clinical trials (RCTs) demonstrated efficacy of HIPEC in patients with AEOC[6,21].

A RCT by Spiliotis et al.[21] highlighted a significant survival benefit for patients with both platinum sensitive and platinum-resistant recurrent OC treated with HIPEC. Unfortunately, the study design, sample size, patient populations and choice of treatment limited the significance of this RCT results.

Recently a randomized phase III trial about HIPEC in AEOC treatment was published by van Driel et al.[6] This RCT, in which after neoadjuvant chemotherapy patients were randomized to undergo IDS with or without HIPEC, showed a significant survival benefit for patients receiving HIPEC. Furthermore, HIPEC supplementary to IDS resulted in a longer recurrence free survival (14.2 months vs 10.7 months; p-value 0.003) and OS (45.7 months vs 33.9 months; p-value 0.02) with a similar rate of grade 3 or 4 adverse events. Furthermore, there was no significant TTC delay between patients who underwent interval cytoreductive surgery with HIPEC and those who underwent surgery alone.

Despite the encouraging results of the last mentioned study, many authors have expressed perplexity about the routinely use of HIPEC in clinical practice. In particular, several criticisms have been raised regarding increased toxicity, costs and the non-reproducibility of the procedure in centers with limited experience with HIPEC[22, 23].

As already other authors suggested, van Driel's et al.[6] RCT is a very important first step toward the clinical introduction of HIPEC, but should not drive changes in practice yet. At the same time, not all the criticisms are justified[22,23]. Regarding the supposed underreported toxicity, the trial showed no difference in terms of grade 3 and 4 adverse events and health related quality of life in the two groups. Moreover, the low renal toxicity in patients treated with HIPEC was due to the use of sodium thiosulfate that determined the selective inactivation of the hydrolysis products of cisplatin responsible for the toxic effect[24]. These results are consistent with data from other scientific literature, showing that the incorporation of HIPEC to cytoreductive surgery seems feasible with only minimal additive toxicities and that morbidity is mainly determined by surgical procedures performed and not by HIPEC itslefe[25]. As for example, a prospective phase II study reported an overall complication rate of 35% and the morbidity rate dropped from 45% to 15% according to the learning curve of the surgeons (p-value 0.024) after stratifying the analysis by the enrollment period[26].

Yet, little is known about the economic impacts of HIPEC treatment. A recent cost-effect analysis by Behbakht et al[27] demonstrates an incremental cost-effectiveness ratio of $ 25.492 per life saved, treating AOC patients with HIPEC after neoadjuvant chemotherapy and interval debulking surgery with an OS of 46 months. A first simple cost estimate for the additional treatment with HIPEC of AOC patients in our hospital, would result in a cost increase up to € 2500 compared to surgery alone. **Table 4**.

Another aspect regards the possibility to introduce HIPEC to chemotherapy treatment including new drugs, like bevacizumab, PARP-inhibitors or immunotherapy. Lately Paris et al[28] published the results of a phase II study in which 40 patients were treated with HIPEC followed by first-line therapy with bevacizumab. Only mild early and late complications, more specifically 19.5% of early G3-G4 complications and none late G3-G4 complications were reported. Moreover, subsequent chemotherapy was administered in all cases and concomitant and maintenance bevacizumab was administered in

Table 4
Comparison of average costs per patient undergoing surgery plus HIPEC or surgery alone in our institution

	Surgery plus HIPEC	**Surgery**
All cases	40	80
OR occupancy min (median) (range)	480 (360-740)	370 (220-545)
Post Operative stay (median)(range)	8	6
	(5-30)	(5-15)
ICU (median)(range)	1 (1-3)	0 (0-3)
Mean cost for each case	10.000 €	7.500 €
The mean increase in cost with HIPEC	+ 2.500 €	

the majority of cases. This research underlined PDS with HIPEC is feasible as well as safe and can be combined with an upfront therapy of AEOC, consisting of primary debulking surgery and carboplatin-paclitaxel-bevacizumab chemotherapy.

Interestingly, a positive interaction was noted between HIPEC and PARP-inhibitors as shown by several studies. Safra et al[29] published a case control study showing CRS with HIPEC in BRCA positive patients with recurrent ovarian cancer improves PFS (20.9 months vs 12.6 months; p-value 0.048).

In addition, hyperthermia enhances DNA-damage induced by chemotherapy with PARP-Inhibitors (PARP-I)[30] and the combination therapy of hyperthermia plus PARP-I would be effective for all patients with PARP-I regardless of their BRCA status[31].

Finally, several studies suggest an immunostimulatory role of HT, connected with a direct stimulatory effect on dendritic cells and indirect effects related to HSP which are potent immune modulators and can stimulate both the innate and adaptive immune responses to tumors[32,33].

An important new step in the validation of HIPEC could emerge from the results of undergoing new RCTs. The Chorine trial, with a similar study design as the van Driel's trial, aimed to compare CRS alone versus CRS in combination with HIPEC, administering intra-peritoneal cisplatin and paclitaxel in patients with stage IIIC OC undergoing neoadjuvant chemotherapy. The HORSE trial (NCT0137895) by the Italian MITO group randomized patients with platinum sensitive recurrent OC, undergoing secondary cytoreductive surgery (SCS), to standard treatment versus HIPEC. The results of several ongoing trials, as the CHIPOR Trial- NCT01376752, HIPECOV Trial-NCT0337169, HIPOVA-01 Trial-NCT03220932 and HIPECOVA Trial-NCT 02681432, available from: https://clinicaltrials.gov/ct2/s?cond=HIPEC+ovarian+cancer&term=&cntry=&state=&city=&dist=) and the next year PSOGI group consensus meeting on IP-therapies in advanced OC could clarify the importance of HIPEC, defining new guidelines for its clinical use.

CONCLUSION

In conclusion, HIPEC has a strong biological and pharmacological rationale in AEO, whose natural history involves mainly the peritoneal cavity. We consider the combination of HIPEC plus surgery as feasible and safe in both primary and recurrent settings. Clinical data on HIPEC appears to be encouraging, but they are mainly derived from retrospective and case-control studies. The positive RCT results in the NACT setting, suggest HIPEC importance in AEOC.

However, it remains unclear which subset of patients may benefit mostly from HIPEC. Therefore, a challenging task for gynecologic oncologists is to design trials for OC treatment involving HIPEC in combination with several new drugs in order to identify the most advantageous and safest therapy approach.

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