Role of hyperthermic intraperitoneal chemotherapy in ovarian cancer

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Abstract: Epithelial ovarian cancer (EOC), has the highest worldwide mortality of all gynecological tumors, in 75% of cases is diagnosed in advanced stages. Despite of treatments with maximal cytoreductive surgery (CRS) and platinum-based chemotherapy (CT), approximately 70% of patients with advanced-stage disease relapse within 18 months, given this high number of recurrences, new approaches are needed to improve outcomes for these patients. Hyperthermic intraperitoneal chemotherapy (HIPEC) has fundamentally changed the treatment of patients with ovarian cancer, with complete CRS and locoregional administration of chemotherapy. The purpose of this review is to find the most relevant, reliable published evidence of the use of HIPEC in ovarian cancer, together with an overview of peritoneal carcinomatosis (PC), procedures, therapeutic approaches in first-line and recurrent disease, the benefit of hyperthermia, selection of the ideal patient for the HIPEC procedures as well to analyze the disease free survival (DFS), morbidity, mortality and overall survival (OS) in patients with ovary cancer. So far, the small amount of evidence points favorably to the use of CRS and HIPEC as a first line of therapy, but more prospective randomized trials are needed to officially adopt this procedure as a standard of care, additionally patients need to know this option exists.

Keywords: Ovarian cancer; hyperthermic intraoperative chemotherapy (HIPEC); prospective; retrospective; rationale; clinical trials

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Introduction

Epithelial ovarian cancer (EOC) has the highest worldwide mortality (1) of all gynecologic tumors. In 75% of cases, EOC is diagnosed in advanced stages, III and IV. In the past 20 years, the 10-year survival rate with advanced-stage has ranged from 10 to 15 % without any noticeable change (2). Approximately 70% of patients with advanced-stage disease relapse within 18 months (3) despite the availability of treatments with maximal cytoreductive surgery (CRS) and platinum-based chemotherapy (3). Historically, peritoneal carcinomatosis (PC) accounts as a damaging cancer, with a very poor prognosis. Therefore, the development of new approaches is critical to improve the outcome for these patients.

The concept of hyperthermic intraoperative chemotherapy (HIPEC) was introduced by Spratt *et al.* from Louisville, KY in 1980 (4). In 1983 the pharmacologic advantages of intraperitoneal drug delivery were exposed by Dedrick plots (5), Koga *et al.* (6) studied the physiology of HIPEC with mitomycin C (MMC) in gastric cancer, Gilly *et*

al. showed the possible benefits of hyperthermia regarding the surgical procedure. The description of peritonectomy is a contribution from Professor Sugarbaker (7). Researchers from all over the world, specially France (8), Italy (9), Japan (10), Latin-America (11), Australia (12), UK (13), Greece (14), Deutschland (15) and Spain (16), are investigating and using CRS and HIPEC as the relatively new standard treatment for PC (17). The 40-year evolution of a "new" and successful multidisciplinary treatment strategy for PC it is an indisputable fact (18). The attempt in this review, is to classify patients in the following groups according to their therapeutic approach (first-line treatment, with or without neoadjuvant chemotherapy (NACT), progression, and recurrence under platinum sensitive or resistant cancer) and thus obtain the most reliable information for each moment of the disease.

Basis of HIPEC

CRS (currently defined as complete macroscopic resection), in addition of systemic chemotherapy (CT) with a platinum-taxane-based compound, is the standard treatment of advanced ovarian cancer (19). Regardless of cancer recurrence, the disease remains limited to the peritoneal cavity for a long time, which represents an optimal target for aggressive regional treatments (20). Loco-regional administration of CT increases the concentration of the chemotherapeutic agent at the site of action, reducing the systemic toxicity of the intravenous (IV) treatment, with the disadvantage of increased postoperative morbidity due to the surgical procedure.

Tumor cells in contrast to normal tissue, can be irreversibly damaged when exposed to high temperatures, by several action mechanisms that in combination with CT increase cancer cells mortality rates.

Physiopathology of carcinomatosis

In the past, it has been assumed that intra peritoneal (IP) cancer dissemination is a random process. However, observations have suggested patterns of cancer cell dissemination by contiguity, but discontinuous. That is, it remains only in the peritoneal cavity, but not as a progressive growing tumor or plaque from the malignancy primary site (21).

Directions taken by detached cancer cells within the peritoneal cavity may be affected by factors including: anatomic site of the primary tumor, histologic type, changes in intra-abdominal pressure, gravity, peristalsis, peritoneal adhesions, fibrin entrapment from trauma during a surgical intervention, resorption, viscosity and volume of peritoneal fluid (22).

Peritoneum basics

(I) Physiopathology of peritoneal dissemination starts with the loss of cell-adhesion from the primary tumor in order to migrate to distant sites. Then, released tumor cells exhibit decreased adhesion and enhanced motility; (II) once the cells are inoculated in the peritoneal cavity, distribution throughout the abdomen begins, directed by three basic forces: gravity, peristalsis, and negative pressure exerted by the thorax and diaphragm movements; (III) successive IP metastasis takes two routes denominated, trans-mesothelial and trans-lymphatic; (IV) the cytokines IL (interleukins), epidermal growth factor (EGF), hepatocyte growth factor (HGF), vascular endothelial growth factor-C (VEGF-C) influences the contraction of mesothelial cells, thereby exposing the sub-mesothelial basal membrane; (V) allowing tumor cells to adhere through the interaction of integrins; (VI) also degrading the peritoneal blood barrier assisted by matrix metalloproteinases (MMPs), and (VII) other motility factors (23-26) (*Figure 1*).

Cytoreduction/peritonectomy

First line treatment at FIGO stages III and IV

The earliest evidence to support CRS, came from Griffiths' retrospective review (1975). In the most recently published study by Biacchi *et al.* (27), two study groups were compared, first one with CRS and HIPEC, second one with NACT followed by CRS and HIPEC as a first-line treatment. Their results reported similar outcomes in both groups regarding PFS of 29.5 months (95 % CI, 25.89–NA months) versus 20.3 months (95% CI, 15.2–28.3 months). Moreover, the OS analysis showed improved outcomes, although not significantly better, in patients who underwent up front surgery than in those in the second group with a median month of OS not reached in the first group *vs.* 51.5 months (95% CI, 33.9–NA months), in the second group. This study draws attention to the better outcomes in patients with complete CRS [Complete Cytoreduction (CC) Score 0], within PFS or OS. The cox univariate analysis showed that patients who underwent CRS with residual disease had approximately 20% higher risk of recurrence than those without residual disease (HR, 1.209,

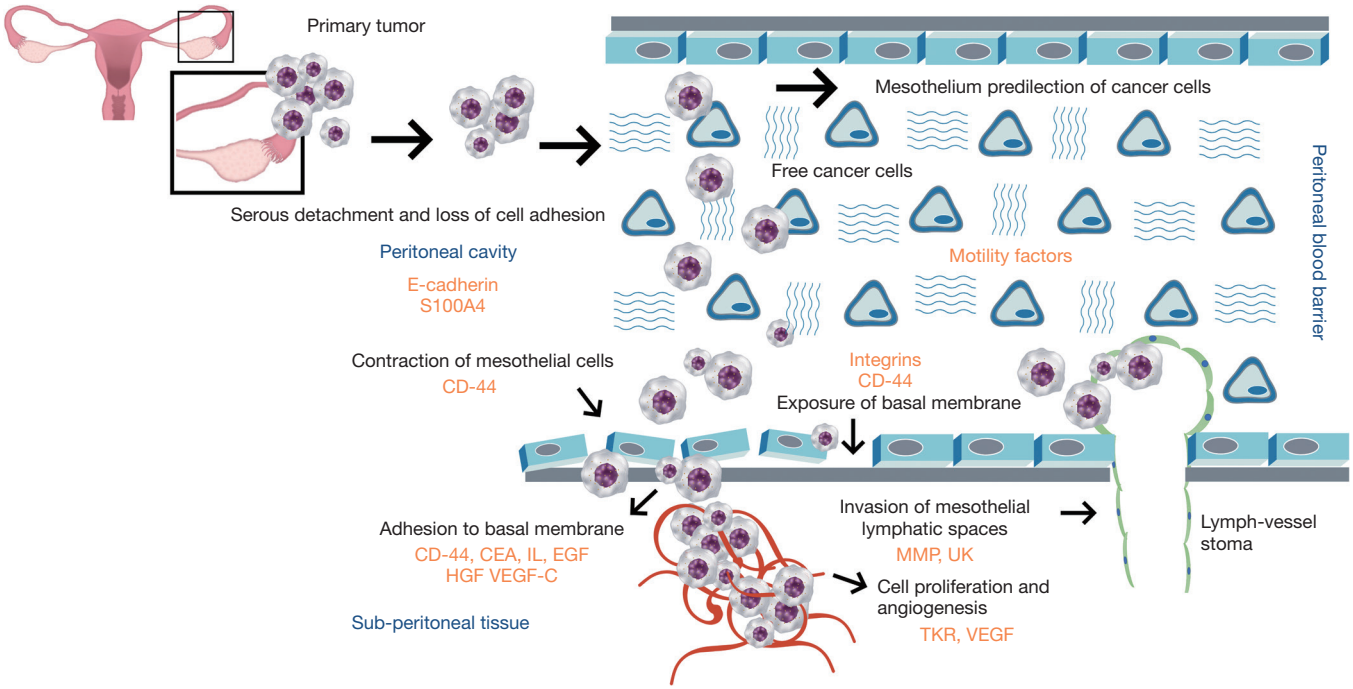

Figure 1 Physiopathology of carcinomatosis.

95% CI, 0.7764–1.882) with increased likelihood of death approximately 50% (HR, 1.562, 95% CI, 0.9332–2.614) (27,28). Bristow's 2006 meta-analysis (22 cohorts with 835 patients) stated that the best first-line ovarian cancer approach is the optimal cytoreduction, these data being corroborated by Dennis S. Chi, GOG 52, 97, and Karin K. Shih.

The "HIPECOVA" study by Campos *et al.*, evaluated the use of HIPEC with paclitaxel (PTX) for patients with recurrent or primary advanced EOC, with two study arms, first: CRS + HIPEC with PTX, followed by postoperative systemic CT with carboplatin (CBDCA) + PTX, and second: CRS followed by postoperative systemic CT with CBDCA + PTX. Their primary outcome measures are OS and PFS, but results are pending to be published. (NCT02681432) (Apendix 1).

Interval CRS—neoadjuvant treatment (NACT)

The name NACT has been portrayed in two different perceptions: number one, is the implementation of CT, after cancer confirmation through just biopsies, following several courses of this systemic therapy, CRS is attempted in the course of an interval laparotomy. Number two is the CT applied after a suboptimal debulking tumor surgery, followed by a CRS called interval CRS, this approach more commonly called as induction therapy, but has also been named 'neoadjuvant' (29).

The concept of primary CT with a posterior interval debulking CRS, has arisen mainly because optimal cytoreduction can only be achieved in 35–50% of women with advanced EOC (30). And without optimal cytoreduction, prognosis at a 5-year survival rate will be of approximately 15%, independent of the residual tumor extension (31).

Ignace Vergote in 2010 stablished the use of neoadjuvant CT as an optimal treatment option in patients with ovarian cancer stage IV (vergote y CHORUS).

The advantages of surgery after NACT are: less intraoperative blood loss, shorter operative time, fewer intensive care unit (ICU) admissions, and a shorter hospital length of stay (LOS). This is especially relevant in countries with limited resources on ICU care, hemotransfusion capacity and advanced post-surgical care measures (32). NACT used for two or three cycles may reduce disease load and improve tumor resectability. Cascales-Campos *et al.* stated that patients with NACT plus complete CRS and HIPEC were associated with a prolonged PFS in all subgroups except those with undifferentiated tumors, compared to control arm of patients without HIPEC (33,34).

The main study on NACT and HIPEC is a work of

van Driel *et al.*, concluding that the addition of HIPEC to interval CRS showed longer recurrence-free survival (RFS) and OS than surgery alone, without resulting in higher rates of side effects. The median RFS was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. The median OS was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group (35).

In this context, there is a phase III clinical trial, the CHORINE study, by Ansaloni *et al.*, assessing HIPEC as upfront treatment of stage IIIC EOC, where they compared unresectable disease, with a partial or complete response after 3 cycles of first line CT (CBDCA + PTX) followed by CRS and HIPEC, with CDDP + PTX versus CRS alone, their results are still pending to be published. (NCT01628380) (Apendix 1).

Recurrent disease

Throughout history, the use of HIPEC in any cancer has been subjected as the introduction of a new therapy inaugurated by the patients with the most unfavorable prognosis, poor outcomes in spite of multiple lines of systemic chemotherapy, with the attempt to rescue them from an imminent death. It is challenging to assess an objective response on recurrent disease together with the comparability between studies, groups and patients; nevertheless, results have been consistently the same, there is a benefit in patients treated with HIPEC.

Obstacles in establishing HIPEC as a standard of care in ovarian cancer have been the discrepancies between studies and published data where patients are included in non-comparable groups. This leaves an unclear role in first-line treatments with or without NACT, or if the studied patients were sensible to platinum agents or non-responders, and in their final analysis there is lack information about OS and DFS or if patients were on their first or second recurrence.

Whereas the beneficial impact of CRS is clear in the first line treatment, it is less evident in the treatment of patients with recurrent disease. Undoubtedly patients with a good performance status, a prolonged disease-free interval, a low carcinomatosis index, an absence of ascites, and optimal cytoreduction are the best candidates for the use of HIPEC (36).

In 2004, Ryu *et al.* pointed the benefit of HIPEC on the recurrent-disease patient group (37). Adding HIPEC to the present treatment modalities for recurrent ovarian cancer seems to improve survival rates in some series, with an acceptable mortality rate, but at the cost of significant morbidity rates during the first few years of the surgical learning curve. The beneficial impact of secondary cytoreduction in the treatment of recurrent disease has not been fully elucidated. Available data, reports consistent survival rates using the combined treatment approach on patients with recurrent EOC (38-47).

In that respect, the CHIPOR study which is an ongoing phase III, European multicentric randomized trial by Classe *et al.*, treating patients in their first relapse of EOC, starting with 2 types of second line intravenous chemotherapy (IVCT), if there is a favorable response, and CRS seems possible, 5 to 8 weeks later patients will be randomized to either treatment A, maximal CRS without HIPEC or B: maximal CRS with HIPEC, with the goal to improve the median OS by 12 months after the patient's first relapse; results have not yet been described. (NCT01376752) (Apendix 1).

There are more retrospective studies with comparison between first-line therapy and recurrent disease, showed in *Table 1*. Prospective studies that describe recurrent disease results, Cotte 2007 (40), Muñoz-Casares 2009 (48), Ansaloni 2012 (45), Gonzalez Bayon 2013 (44) are showed in *Table 2*.

Pharmacokinetics and pharmacodynamics of drugs

Hyperthermia is known to enhance cytotoxicity and improve the penetration depth of some cytostatic drugs (49). Conclusions from studies have given us information about the area under the curve (AUC) of intraabdominal used doses, exposure time of Melphalan, Mitomycin C and CDDP as well as the expected toxicity (50-52).

The data obtained from these studies have set the standard for their use, but it has been remarkably challenging to assume they are completely valid, due to the multiple factors that affect the results, i.e., the complexity of establishing the desirable drug concentration (53).

So, the rationale for IP drug administration is supported by preclinical and pharmacokinetic data; Armstrong *et al.*, showed a considerable toxicity with the administration of normothermic IP CDDP in association with PTX (54). In the hyperthermia studies this is not observed when CDDP is administered alone or in association with MMC which is favorable for maintaining peritoneal drug concentration at therapeutic levels.

Hyperthermia is found to be a powerful modulator of CDDP cytotoxicity, both in sensitive and resistant ovarian cancer cells. Relatively high heat doses (43 ℃ during 60 min) appear to specifically interfere with CDDP cell

Table 1 Retrospective HIPEC scientific evidence

Author	Year	Study	Platinum status	Disease setting	HIPEC Moment	No. Patients (HIPEC)	Complete cytoreduction (%)	Morbidity (%)	Mortality (%)*	DFS (m)**	OS (m)**	5-year OS (%)	PO treatment	HIPEC drug
Ryu KS	2004	Case-control in a cohort study	NA	First line	CRS + Adj CT + HIPEC Adj	57	84.2 *vs.* 80	29.8 *vs.* 11.6	NA	48.7 *vs.* 19.8	NA	76.1 *vs.* 62.9	NA	CBDCA/ INF-a
					CRS + Adj CT + CRS	60								
Raspagliesi F	2006	Case series	Sensitive	First line & Recurrent	CRS + CT + HIPEC	40	82.5	5		23.9 (FL) *vs.* 10.5	41.4 (FL) *vs.* 31.5	15	NA	CDDP+ MMC *vs.* CDDP + DOX
Bae JH	2007	Case-control in a cohort study	NA	First line/ Recurrent	CRS + CT (6-12c) + HIPEC	67	71.6	39	NA	74 *vs.* 17	31 *vs.* NR	70.4 *vs.* 31.3	3c *vs.* 6c	CBDCA *vs.* TAX
					CRS +CT (6-12c)	29								
Di Giorgio A	2017	Case series	Sensitive	First line/ Recurrent	CRS + CT + (recurrent) CRS *vs.* (First line) CRS + HIPEC	47	59.6	21	4	27.4	30.4	17	CT	CDDP
Bereder J	2009	Case series	Sensitive	Recurrent	NA	246	66.6	12	0.4	0.13	49	35	NA	CDDP/DOX/MMC
			Resistant	Recurrent		62								
Pavlov MJ	2009	Case series	Sensitive	First line	CRS + HIPEC	31	92.8	15	3	0.262	38.1	67	NA	CDDP/DOX
				Recurrent	CRS + HIPEC	25								
Chua TC	2009	Systematic review	Random	First line/ Recurrent	Random	895	NA	28.8	2.9	10 to 57	Random	12 to 66	NA	CDDP, MMC, DX, CP
Fagotti A	2012	Case-control	Sensitive	Recurrent	CRS + HIPEC *vs.* CRS	30	97	NA	0	26 *vs.* 15	NA	68 *vs.* 42.7	CT	OXA
Warschkow R	2012	Case series	Sensitive	First line/ Recurrent	CRS + HIPEC	21	90.5	28.6	0	NA	NA	72.5	NA	CDDP
Bakrin N	2012	Multicentric case series	Sensitive	Persistent + Recurrent	CRS + HIPEC	246	92.2	11.6	0.37	12.8	48.5	35	NA	CDDP or CDDP + DOX or CDDP + MMC
Bakrin N	2013	Multicentric cohort	Sensitive	First line	CRS + HIPEC	92	NA	NA	NA	11.8	35.4	17	NA	CDDP/OXA/DOX/MMC
			Sensitive	Interval	CT + CRS + HIPEC + CT									
			Sensitive	Consolidation	NACT + CCR + HIPEC									
			Resistant	Persistent	CRS + HIPEC	474				NA	NA	NA		
			Sensitive	Recurrent	CRS + HIPEC					NA	45.7	37		
			Resistant	Recurrent	CRS + HIPEC									
			Sensitive/ Resistant	2nd recurrence	CRS + HIPEC									
Biacchi D	2019	No Randomized	Sensitive	First line	CRS + HIPEC	34	73.6	22.9	2.1	29.5 *vs.* 20.6	NR *vs.* 51.5%	NA	NA	CDDP
					NACT + CRS + HIPEC	110								

*, mortality in the 30-day post-operative period; **, numbers expressed in months except specified otherwise, published information only available in percentages. HIPEC, hyperthermic intraperitoneal chemotherapy; R, retrospective; P, prospective; DFS, disease free survival; OS, overall survival; PO, post-operative; NA, not available; CRS, cytoreductive surgery; Adj, adjuvant; CT, chemotherapy; NACT, neoadjuvant chemotherapy; NR, not reached; FL, front line; m, months; y, years; c, cycles; INF-a, interferon alpha; CBDCA, carboplatin; CDDP, cisplatin; MMC, mitomycin-C; DOX, doxorubicin; OXA, oxaliplatin. Abbreviations according to the National Cancer Institute drug dictionary. Available online: https://www.cancer.gov/publications/dictionaries/cancer-drug

Table 2 Prospective HIPEC scientific evidence

Author	Year	Study	Platinum status	Disease setting	HIPEC Moment	No. Patients (HIPEC)	Complete cytoreduction (%)	Morbidity (%)	Mortality (%)*	DFS (m)**	OS (%)**	5-year OS (%)^	PO treatment	HIPEC drug
Cotte E	2007	Case series	Sensitive/ Resistant	Chemoresistant	CRS + HIPEC	81	55.5	13.6	2.5	19.2	28.4	NA	CT	CDDP
				Recurrent	CT + secondary CRS + HIPEC									
				Second recurrence										
Muñoz-Casares FC	2009	Case series	Sensitive		CRS + CT + (recurrent) CRS/ HIPEC	14	64	29 *vs.* 25	NA	48±42 *vs.* 24±21	67 % *vs.* 29 %	67	6c (CDDP or CBDCA + TAX)	TAX
					CRS + CT + (recurrent) CRS	13								
Guardiola E	2009	Case series	Sensitive	First line	CT + CSR (HIPEC) *vs.* CRS (HIPEC)	47	57	77		14	NA	NA	CBDCA + TAX	CDDP
Pomel C	2010	Non-randomized	Sensitive	Consolidation	CRS + CT + HIPEC	28	NA	46.4	NA	NA	0.67	NA	NA	OXP
Deraco M	2011	Case series	Sensitive	First line	CRS + HIPEC	26	56.6	15	4	30	NA	60.7	6c (CBDCA + TAX)	CDDP + DOX
Ansaloni L	2012	Randomized	Sensitive	First line/ Recurrent	CRS + HIPEC *vs.* CRS	39	90	18	NA	11.7	36	NA	CT	CCDP +TAX *vs.* CDDP +DOX
Gonzalez Bayon L	2013	0	Sensitive	First line	CRS + HIPEC	15	73	26	2	21.1	0.72	77.8	NA	CDDP + DOX
		Case series		Recurrent	CRS + HIPEC	19	74	26	1.9	18.1	0.622	62.8	NA	CDDP + DOX
				Second recurrence	CRS + HIPEC	8	75	26	0.8	5.7	0.179	35.7	NA	CDDP + DOX
Spiliotis J	2015	Randomized	Sensitive/ resistant	Recurrent	CRS + HIPEC	60	65	NA	NA	NA	26.7	NA	NA	CCDP + TAX
					CRS + CT	60	65	NA	NA	NA	13.4	NA	NA	DOX + TAX or MMC
Lim MC	2017	Randomized	Sensitive	First line	CRS + HIPEC	92	1	NA	0	0.209	0.51	NA	NA	CDDP
					NACT + CRS + HIPEC					0.372	0.479			
					NACT + CRS	92				0.295	0.277			
					CRS					0.16	0.494			
Van Driel W	2018	Randomized	Sensitive	First line	NACT + CRS	123	67	25		10.7% *vs.* 14.2%	33.9% *vs.* 45.7%	NA	NA	CDDP
					NACT + CRS + HIPEC	122	69	27						

*, mortality in the 30-day post-operative period; **, numbers expressed in percentages except specified otherwise (months), the first OS column does not specify the timeline. ^, this column shows the % of published data specific to 5 year overall survival timeline. Abbreviations according to the National Cancer Institute drug dictionary. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug. HIPEC, hyperthermic intraperitoneal chemotherapy; R, retrospective; P, prospective; DFS, disease free survival; OS, overall survival; PO, post-operative; NA, not available; CRS, cytoreductive surgery; Adj, adjuvant; CT, Chemotherapy; NACT, neoadjuvant chemotherapy; NR, not reached; FL, front line; m, months; y, years; c, cycles; INF-a, interferon alpha; CBDCA, carboplatin; CDDP, cisplatin; MMC, mitomycin-C; DOX, doxorubicin; OXA, oxaliplatin.

resistance, this mechanism has not been fully elucidated. The following proposed mechanisms of resistance to CDDP are mostly a result from the studies by Hetting *et al.*: drug accumulation, decreased detoxification, increased CDDP-DNA adduct formation, reduced DNA repair, and modulation of CDDP resistance. The intention of HIPEC treatment is to reverse, avoid or modify these mechanisms in order to achieve response rates that grant the patient prolonged RFS, this is also demonstrated in a study by Spiliotis *et al.* (14).

Hyperthermia

In vivo tumor cells in contrast to normal tissue, can be irreversibly damaged when exposed to temperatures between 40º and 44º, due to the tumor's physiological characteristics. The vessel distribution of solid tumors is chaotic and inadequate, mediating hypoxic and acidic regions (55) making cells more vulnerable to the hyperthermia treatment. With temperatures after 42.5–43 ℃ and time of exposure, are contributing factors to the hyperthermia therapy efficacy. Most normal tissues remain unaffected even after an exposure of 1 hour at a temperature of up to 44 ℃ (56). The central cell death mechanism with hyperthermia is protein denaturation, observed at temperatures >40 ℃, altering structures like the cytoskeleton and cell membranes, affecting DNA synthesis and repair mechanisms (57). Several studies have used hyperthermia treatment alone, one series of 343 patients reported complete response rates varying from 0% to 40% (overall 13%) and partial response rates from 0% to 56%, with an overall objective response rate of 51%. Along the same line, three additional studies report complete response rates of 11%, 16% and 18% respectively (4,58).

Selection of the ideal patient

Nowadays, we don't have a randomized clinical prospective trial that gives us the best explanation to select the ideal patient. We utilize the following scores as a tool for patient selection, taking in to consideration all three of them added to the oncological team experience in order to obtain the maximal benefit for the patient, which is optimal cytoreduction, less morbidity, no postoperative mortality, increase in PFS and OS.

Peritoneal carcinomatosis index (PCI)

The tumor volume found at the time of surgery has proven to be a prognostic factor and allows preparation of treatment schemes, the following have been published:

The Gilly PC staging (59), the Simplified Peritoneal Cancer Index (SPCI), mostly used for colorectal and appendiceal cancer staging with a prognostic implication for survival, following CRS and HIPEC (60). The Peritoneal Cancer Index (PCI), which was initially used for the evaluation of carcinomatosis of gastrointestinal origin (61). In EOC is determined at the time of surgical exploration, functioning as a complete cytoreduction probability estimate and has been shown to be an accurate assessment survival tool with the treatment combination of CRS and HIPEC (62). With the advantageous, ease of use and accuracy to correlate with the possibility of optimal cytoreduction and OS has directed its examination in ovarian cancer, also obtaining an extraordinary correlation (63-65).

Peritoneal Surface Disease Severity Score (PSDSS)

The development of tools capable of defining more clearly the current status of an individual, based on preoperative clinical characteristics not only helps us to improve patient selection who will benefit from the HIPEC procedure, but also to discuss the possible risks with patients (66). PSDSS was developed to prospectively stratify patients [based on (I) symptoms, (II) disease extent (CT-assisted PCI), and (III) histology], evaluated with peritoneal disease from colon cancer, and on a multivariate analysis was found to be a prognostic predictor of survival (67,68).

Due to the effectiveness of the score in colon cancer, PSDSS was performed by Esquivel *et al.* in patients with carcinomatosis taken to HIPEC treatment in ovarian cancer. Patients with score of I/II, showed a survival advantage over patients stratified as III/IV regardless of therapy, 100 versus 55 (68). In the original paper (for colon cancer) patients were stratified according to; (I) symptoms, described from none to severe, (II) the PCI, from less than 10 to more than 20, (III) histology type/tumor differentiation. In the ovarian paper, the PSDSS score obtained a P value of 0.001 between groups. An important point worth mentioning is that the presence of signet ring cells is extremely rare in ovarian cancer, so it would be worth to study patients whose histological findings present clear cells instead.

Fagotti index

Therefore, knowing if we can take patients to complete cytoreductions (CCR0) is crucial. Diagnostic image studies (69)

have shown failures in this regard to calculate the PCI, or establish the severity score; for this reason, Fagotti *et al.* designed a laparoscopic evaluation. this calculates with greater certainty, avoids unnecessary laparotomies and helps to start earlier with systemic therapy. Eight laparoscopic features are assessed as potential indicators of surgical outcome; (I) the presence of ovarian masses (unilateral or bilateral), (II) omental cake or bulky lymph nodes, (III) PC, (IV) extensive carcinomatosis of the diaphragm, (V) mesenteric retraction, (VI) bowel infiltration, (VII) stomach infiltration, (VIII) liver metastasis (70-72). This index it's the most practical one to understand what is happening in the peritoneum. Eighty-seven percent of the candidate patients for debulking according to this index had optimal cytoreduction, only 13% did not, and this was due to the presence of retroperitoneal disease. Since her pilot study was published, this index has displayed the feasibility, accuracy and efficacy needed to assess whether the patient could be a candidate for optimal cytoreduction with a (PPV) positive predictive value and a (NPV) negative predictive value between 80% and 100%.

Worldwide experience with the use of HIPEC

The tables above, depict the highly relevant published studies with evidence that supports our daily practice, the majority showing a beneficial effect of HIPEC use in ovary cancer. Nevertheless it is to be noted that the reason why HIPEC has not been established as a standard of care in ovarian cancer is a attributable to the discrepancies between published data, with non-comparable patient groups, unclear first-line treatments with or without NACT, not stating if the patients were sensitive to platinum agents or non-responders, furthermore the available results of OS and DFS lack information about timing, meaning if patients are on their first or second recurrence, which continues to be a drawback in this field of research. For the retrospective data (28,34,37,38,72-80), for prospective data (27,35,36,40,44,45,48,81,82) (*Tables 1,2*).

Quality of life (QoL)

For many years, the measurement of the QoL in patients undergoing a HIPEC procedure, was not a fundamental objective, the first pursued information in a new treatment is to find usefulness with respect to DFP and OS.

QoL returns to a primary objective with the evidence of treatment benefits, now in published studies describing the patient's point of view, outlining if the benefits outweigh the risks and qualifying if the discomfort presented is compensated or bearable when compared to the benefit of being alive. In 2013, Tan *et al.* (83), describes QoL based on the European Organization for Research and Treatment of Cancer (EORTC) questionnaires for ovarian cancer, as well as Chia *et al.* (84), Piso *et al.* (85), or Koole *et al.* (86). (OVHIPEC trial), described that in 80% of patients there were no changes in QoL after 6–16 months of HIPEC treatment and denote a clear improvement in cognitive function and fatigue caused by peritoneal disease (P=0.014 and 0.04, respectively). Not much information in this regard is available, but it is also true that every day patients are grateful for these improvements, which, together with surviving a little longer, are the goal of our medical management (86-88).

Cost-benefit

It is apparent that the expense of the HIPEC procedure is by far less expensive than any current systemic CT for ovarian cancer (bevacizumab, olaparib, niraparib or rucaparib), it is also clear that systemic therapies are ineffective for PC. There are few studies in this field, mostly with non-encouraging results, yet the surgical community are motivated to keep going due to clinical improvement, the increase in DFS and OS. Adding up these aspects together toward a specific patient, we observe how a small window of opportunity transforms in a big door where the patient can comfortably pass.

The costs of a HIPEC procedure can not only be accounted as the intraoperative costs, since the post-surgical costs can be more significant, depending on the length of stay in the ICU, which is variable in every patient, some don't require it and some can stay in the ICU up to 30 days if presented with complications such as pneumonia, pleural effusion, kidney failure, surgical wound infection, anastomosis dehiscence, stomata, hydro electrolytic abnormalities, and cardiac or hematological complications (89-91).

The benefit of the HIPEC procedure when compared to systemic therapies, is that it only needs to be performed once, unlike systemic therapies used as the only treatment modality involve not only the expense of the drug itself, premedication as support therapy to avoid chemotherapy adverse effects, also the expense of hospital transport every time it needs to be administered , and this cost is not only for one person, as generally patients are accompanied by a significant other who had to stop a working day or daily

activities to assist the patient receiving the therapy. All these expenses are not commonly appreciated, but have a long-term impact on therapeutic adherence (92-96).

Conclusions

In a 2002 editorial in the *Journal of Clinical Oncology*, Alberts *et al.* (97) stated, "We cannot think of any other setting in oncology where the results of three positive phase III trials have not led to widespread adoption of the superior therapy. The time has come for IP chemotherapy to move beyond the setting of clinical trials and into the standard treatment armamentarium for women with optimally debulked stage III ovarian cancer, we owe our patients nothing less." That being said, our task is to look forward, not backwards, in terms of how we can prolong the lives of these extremely courageous women with advanced ovarian cancer who fight every day to stay alive.

The discussion of whether one treatment is better than another, should not fit into this gynecological neoplasm, which, historically is the deadliest. the discussion should emphasize in what treatment sequence will break the 50% 5-year survival rate barrier, as well as the 80% of recurrences and the 94% of 10-year mortality for these patients. Adding is far better than arguing.

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Supplementary

Appendix 1 List of ongoing HIPEC Clinical Trials

1. Chang S, Lee J. Comparative Effectiveness of HIPEC Following Interval Debulking Surgery in Patients With Advanced-stage Ovarian Cancer [Internet]. Republic of Korea , july 2019: Ajou University School of Medicine; p. ClinicalTrials.gov identifier (NCT number): NCT03448354. Available online: https://clinicaltrials.gov/ct2/show/NCT03448354?term=NCT03448354&draw=2&rank=1
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3. NARDUCCI F. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer (CHIPPI) (CHIPPI) [Internet]. France, February 2019, multicentric: Centre Oscar Lambret; p. ClinicalTrials.gov identifier (NCT number): NCT03842982, Other Study ID Numbers: CHIPPI-1808 2018-003680-62 (EudraCT Number). Available online: https://clinicaltrials.gov/ct2/show/NCT03842982?term=NCT03842982&draw=2&rank=1
4. Momeni M. Hyperthermic Intraperitoneal Chemotherapy for Recurrent Ovarian Cancer [Internet]. United States, California, March 2019: Loma Linda University,; p. ClinicalTrials.gov identifier (NCT number): NCT02672098, Other Study ID Numbers: 5150302. Available online: https://clinicaltrials.gov/ct2/show/NCT02672098?term=NCT02672098&draw=2&rank=1
5. Jewell A. Heated Intraperitoneal Chemotherapy in Primary Ovarian Cancer Patients [Internet]. University of Kansas Medical Center, July 2019; p. ClinicalTrials.gov identifier (NCT number): NCT03321188, Other Study ID Numbers: IIT-2017-HIPEC-Ovarian. Available online: https://clinicaltrials.gov/ct2/show/NCT03321188?term=NCT03321188&draw=2&rank=1
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