Hyperthermic intraperitoneal chemotherapy (HIPEC): Should we look closer at the microenvironment?

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HIGHLIGHTS:

There is no consensus on hyperthermic intraperitoneal chemotherapy (HIPEC) modalities.

HIPEC has an impact on the whole tumour microenvironment.

HIPEC has both negative and positive effect on tumor environment and its anti-tumoral activity.

ABSTRACT

The age of cancer as an isolated single-cell concept is now behind us. It is now established that epithelial ovarian cancer, like other cancers, interacts with the healthy bystander cells to influence them and takes advantage of their nutritional, immunological, disseminating and other capacities. This interaction has become a therapeutic target, as shown by the numerous studies on this subject. Intraperitoneal chemo-hyperthermia has been part of the therapeutic armamentarium for some time yet its efficiency in ovarian cancer has only been recently proven in a randomized controlled trial. However, its therapeutic performance is not revolutionary and epithelial ovarian cancer maintains a high mortality. In this review, we studied the impact of HIPEC on the microenvironment and vice versa to determine whether it could be the key to this lukewarm efficacy. We began by exploring the modalities of HIPEC and establishing the reasons that make this treatment topical. Then, we examined its impact on each element of the tumour environment to obtain a global view of the resistance mechanisms at work in HIPEC.

Keywords: Ovarian cancer / Hyperthermic intra peritoneal chemotherapy/ Survival / Microenvironment / Resistance

I- Introduction

Hyperthermic intra peritoneal chemotherapy (HIPEC) is a treatment option for patient with abdominal cancer and peritoneal carcinosis, without distant metastasis. It is a combination of three procedures: intra peritoneal drug release, chemotherapy and hyperthermia. It has mainly been evaluated in peritoneal carcinomatosis in colorectal, mucinous appendicular adenocarninoma and ovarian cancer. In the latter, its benefits in terms of overall survival and recurrence-free survival have been showed by van Driel et al. [1] in the first prospective randomized controlled trial, in 2018. Unfortunately, the survival length remains short with a median recurrence free survival of 14.2 months in stage 3 patients with ovarian cancer

undergoing total cytoreductive surgery and HIPEC [2]. There must be an underlying mechanism explaining the resistance of cancer cells to HIPEC.

It has been demonstrated that the tumor cells strongly interact with their microenvironment [3]. Tumoral colonization and proliferation are subject to the permissiveness of the microenvironment of the targeted organ. As a result, the interaction between disseminated malignant tumor cells and their microenvironment is a key mechanism in their progression and metastasis. The tumor microenvironment (TME) is defined as the cellular and molecular components and the mechanical stresses that surround the tumor cells and interact with them [4]. The cellular component of the TME includes for instance stromal cells such as fibroblasts, cells of the immune system and vascular cells. Recently, few studies reported an influence of TME cells on the sensitivity of cancer cells to hyperthermia [5]. Here, we aimed to review the possible role of the TME in the resistance to HIPEC.

II- From hyperthermia to HIPEC

1. Hyperthermia

Hyperthermia therapy is defined by the rising of the human temperature over 38°C. Hyperthermia over 43° was found to have a direct cytotoxic effect *in vitro* in animals[6]. Each cell has a different sensitivity to hyperthermia yet there seems to be a clear thermic threshold. Over 43°C, an exponential cell death occurs. The time needed to obtain this cell death, is correlated to the temperature used. When diminishing the temperature of one degree Celsius, the exposure time must be multiplied by two between 42.5°C and 47°C [7] . There is actually no consensus on the time of exposure and the temperature. In the recent trial by van Driel's team [1], an intraabdominal temperature of 40°C (104°F) was maintained by circulation of the heated saline during 90 minutes whereas in Lee et al. study [8] they used a dextrose solution 1.5% at 42°C for 90 minutes.

Hyperthermia is all about dose. *In vivo,* in a healthy tissue, hyperthermia will increase tissue oxygenation by raising blood flow through decreasing peripheral vascular resistance by mechanical dilation via the smooth muscle cells that cover the microveins [9]. When the temperature exceeds this threshold, on the contrary, the blood flow decreases via fluid shift between interstitial compartments micro-thrombosis and endothelial swelling, resulting in decreased tissue oxygenation and therefore cell death. Damages caused by moderate hyperthermia depends on the type of tissue [10]. Nevertheless, in tumoral tissue, vascular architecture is complex and anarchic with territories in constitutive hypoxia, de facto increasing the sensitivity of the tissue to hyperthermia.

Thus in oncology, whole-body hyperthermia at temperatures over 41.5°C combined with chemotherapy for metastatic cancers is also gradually finding its place in oncology [11].

2. Intraperitoneal Chemotherapy

As ovarian carcinoma is essentially a peritoneal disease, intraperitoneal delivery of chemotherapy enhances drug delivery at the peritoneal surface with theoretical low systemic passage and may improve outcomes. Thus, chemotherapy can be delivered directly through the peritoneum. A Cochrane's meta-analysis included 2119 women and 9 randomized studies comparing intravenous (IV) and intraperitoneal (IP) administration of adjuvant chemotherapy. Intraperitoneal chemotherapy provides a significant gain in overall survival (OS) (8 studies), with a hazard ratio (HR) of 0.81 (95% CI 0.72-0.90). This gain in OS is independent of the number of drugs used or the dose.

The phase III randomized trial of intraperitoneal chemotherapy in ovarian cancer from 2006 [12] compared paclitaxel 135 mg/m^2/24h on day one (D1) and cisplatin 75 mg/m^2 IV on D1 to paclitaxel 135 mg/m^2/24h IV on D1, cisplatin 100 mg/m^2 IP on D2 and paclitaxel 60 mg/ m^{2}IP on D8. Median progression free survival (PFS) was better in the intra-peritoneal (IP) group but

with elevated impact on the quality of life mainly related to the presence of the peritoneal catheter. Many studies have searched for new protocols to increase the tolerance of the peritoneal approach [13,14] mainly by lowering IP Cisplatin doses. Yet, despite these data, IPC has not been accepted as a standard treatment. In order to reduce this toxicity and retain the efficacy, the gynecology oncology group (GOG) designed the GOG-252[15], a randomized controlled trial comparing totally IV route chemotherapy, the former standard treatment with IP Cisplatin and IP Paclitaxel and a third new arm supposed to reduce IP toxicity with IP Carboplatin and IV Paclitaxel; each arm receiving additional treatment with Bevacizumab. No difference in PFS or OS was found. Nevertheless, the authors suggested that Bevacizumab may have compromised the efficacy of the Cisplatin IP arm. Though, considering these data, IP route has little support from the scientific community.

3. Intraoperative intraperitoneal chemotherapy with hyperthermia - HIPEC.

The pharmacokinetic advantage of intraperitoneal chemotherapy is the most important rational for HIPEC in peritoneal surface malignancy. The objective of intraoperative exposure of the peritoneal cavity is to free itself from possible digestive adhesions that could exclude certain territories and increase toxicity. Furthermore, extended resections of the peritoneum and or organs covered by peritoneum do not modify HIPEC pharmacodynamics [16]. Penetration of chemotherapy agents are ideally measured by the area under curve (AUC) which is an integral of concentration over time. An AUC ratio of intraperitoneal concentration to plasma concentration time reflects how much of the drug is preserved in the peritoneal cavity and how much was absorbed by the systemic circulation, the objective is therefore a high AUC ratio.

The agent has to be of large molecular weight and water-soluble, rapidly cleared from the systemic circulation, potentiated by hyperthermia, and must have proven its efficacy in ovarian cancer. Platinum salts have been mainly explored in HIPEC. They have in common the

character of potentiation of hyperthermia [17]. Carboplatin is a well-known and effective IV chemotherapy, recommended as a neoadjuvant agent combined with paclitaxel. Its advantage over other platinum agents in intraperitoneal administration is its higher molecular weight and lower renal toxicity. Still it suffers from a low peritoneal to plasma AUC around 15-20 [18], and therefore, 7 times more platinum could be detected after Cisplatin treatment than after equimolar treatment with carboplatin [19] both in cultured cells *in vitro* and in peritoneal tumors *in vivo*. This is mainly because of the high liposolubility of Cisplatin resulting in an advantageous peritoneal/plasma AUC ratio (20±6). While the price per weight of the two molecules is the same, administered doses of Cisplatin varies from 50 to 120 mg/ m^2 respectively 300 to 1,000 mg/ m^2 for Carboplatin. However, pharmacokinetic studies favor the use of Carboplatin because its peritoneal clearance is 3 times lower, thus explaining perhaps its better tolerance in IPC. Washing the peritoneal cavity at the end of the procedure frees us from this difference. In the phase 3 randomized OVHIPEC trial by van Driel et al. [1] which provides the basis for the most recent recommendations of gynecological societies; surgery followed 3 IV chemotherapy treatments (carboplatin AUC 6 and paclitaxel 175 mg/ m^2) and the experimental arm consisted in surgery plus HIPEC (Cisplatin 100 mg/ m^2 at 40°C delivered in three doses with nephroprotection by thiosulfate).

In addition to the extreme variability of the drugs and temperatures used, there is no consensus on the HIPEC technique. In a recent review of the current practice in Spanish hospitals [20], 65% of the centers administered HIPEC using a closed system, as opposed to the open system used for example in the Van Driel study, were the debulked cavity is left open. 53% of the surgeons indicated that the infusion temperature of the intraperitoneal chemotherapy solution(s) was 42 °C. Median time of exposure was 90 minutes. The cost it takes to perform HIPEC, excluding the price of running the machine and chemotherapy

agents, was mainly above $4000. Figure 1 is a schematic representation of an open coliseum HIPEC identical to that used in the Van Driel trial [1].

Figure 1 : HIPEC open technique : Coliseum.

Although HIPEC has been used in peritoneal carcinosis for more than 30 years, its use is struggling to find its place. In ovarian cancer, even if the Van Driel trial is a major argument in the decision to offer this therapy to patients, it seems that there is no unanimity, mainly because the gain in survival remains moderate.

It now seems fundamental to reflect on the mechanisms of resistance that could explain this phenomenon, and direct us towards future directions of therapeutic potentiation.

Table 1: HIPEC trials through the last 10 years.

III- Role of the microenvironment in HIPEC

The ovarian tumor microenvironment consists of structural extracellular matrix (ECM) and cellular network. The latter can be divided in endogenous or recruited immune cells, supportive stromal cells such as fibroblasts, endothelial cells and adipose tissue[4]. It has been shown that cancer promotes an inflammatory microenvironment [21]. Chronic inflammation, caused by the proliferation of tumor cells, leads to a paradoxical reaction of the microenvironment that will lead to the proliferation of cancer cells. The aim of this literature review is to describe the interactions of the microenvironment with cancer cells during HIPEC.

Figure 2: Biocellular mechanisms at work in the ovarian tumor microenvironment during HIPEC.

1. Role of the extracellular matrix

Non-cellular components of the tumour microenvironment are composed of the ECM, ECM remodelling enzymes and growth factors. ECM is a specific component of the tumour

174 microenvironment that plays a role in cell attachment, survival, communication, spreading,
175 migration, proliferation and multicellular organisation by a complex mix of architectural,
176 mechanical and biochemical signals [22]. Components of the ECM are called the matrisome,
177 and are grouped into two families: proteoglycans and fibrous proteins [23]. Peptides structures
178 and activities are inherently thermolabile, thermodynamic considerations drive the assembly of
179 these structures (e.g. hydrogen bonding, electrostatic interactions, van der Waals interactions,
180 and the hydrophobic effect) and most proteins are therefore temperature sensitive.
181 Collagen I is one of the main component of the fibrous proteins. Hepatocellular cancer cells
182 (HCC), exposed to a sublethal hyperthermia, and then cultured with collagen I showed
183 accelerated migration and highest invasive profile [24]. Heat shock protein (HSP) 47 is a
184 chaperone of collagen I and its precursors and form a complex in the endoplasmic reticulum in
185 order to protect it from thermal alteration during the transit to cellular surface [25]. The
186 relationship between HSP 47 and collagen I in the response of ovarian cancer to hyperthermia
187 has never been explored before. Could low level of HSP47 be a marker of sensitivity to HIPEC?
188 Proteoglycans are the second type of protein composing the ECM. Among them, versican is a
189 large chondroitine sulfate proteoglycan that belongs to the aggrecan family. Elevated versican
190 levels have been found in many malignant tumours [26]. In epithelial ovarian cancer (EOC),
191 higher levels of versican in the tumoral stroma are associated with a poor prognostic [27].
192 Recently, in a cohort study of peritoneal carcinosis patients treated by HIPEC, high level of
193 versican was associated with a better prognosis, suggesting that the versican could be a
194 predictive marker of the response to HIPEC [28].
195
196 **2. Cellular microenvironment**
197 Cellular microenvironment is constituted of immune, stromal, endothelial, nervous system cells
198 and organ specific cells like mesothelial cells in peritoneal metastasis or epiploon's adipocytes,

and cancer stem cells. They interact with OCC by direct cell-to-cell contact or by secreting soluble factors (chemokines).

i) Mesenchymal stem cells

Mesenchymal stem cells (MSC) are characterized by their three main attributes: stemness, multipotency and self-renewal. They can be isolated from umbilical cord, bone marrow, adipose tissue, peripheral blood, spleen and skin[29]. They can differentiate into cancer associated fibroblasts (CAF), pericytes, osteocytes, adipocytes, chondrocytes and smooth muscle cells in the tumor micro-environment (TME). Their role is to migrate toward damaged tissues and contribute to repair it by cellular support, angiogenesis and modulation of immune cell functions[30]. MSC are drawn to inflammatory environments, such as ovarian cancer, and are therefore numerous in that cancer [31,32]. In line with Paget's theory [33], comparing the cancer cell to a seed and the tissue to soil, MSC would be the fertilizer.

When MSC extracted from bone marrow are exposed to fever range hyperthermia, and co-cultured with macrophage, they switched the profiles of macrophages from pro-inflammatory to anti-inflammatory, increasing secretion of interleukin 10 and lowering tumor necrosis factor alpha [34]. These changes are mediated by heat shock factor (HSF) 1's translocation into the nucleus. HSF-1 is a protein which in its stable form is located in the cytoplasm and bound to HSP 90, HSP 70 and TCP1. In the event of heat stress, HSF-1 releases these molecules whose role is to fold up heat-altered proteins. Once released, HSF-1 passes into the nucleus and activates the transcription of anti-inflammatory proteins, notably cyclo-oxygenases (COX) and prostaglandins synthases (PTGES) but also program death ligand one (PDL-1) (see Figure 2). Finally prostaglandins cause a drop in TNF-alpha secretion and an increase in interleukin 10, orienting macrophages towards an anti-inflammatory profile [34]. In addition, PDL-1 secretion decreases T cell activity.

During hyperthermia, Lis et al showed that after co-culture with MSC in transwell, OCC developed a thermo-resistance at 42 degrees [35]. This relationship appears to be mediated by SDF 1 and its C-X-C chemokine receptor type 4 (CXCR4) receptor whose inhibition by an anti-CXCR4 antibody reverses the survival gain [35] (see Figure 2).

Concerning chemotherapy, the work of Pasquier et al.[21] showed that transwell co-culture of MSC with ovarian cancer cells (OCC) decreased OCC mortality, that this MSC-OCC collaboration was mediated by CCL2 and CCL5 and then in an autocrine loop OCC-OCC by IL-6. These results were verified *in vivo* in a mouse model with an anti IL6 antibody that restored sensitivity to chemotherapy. Recently Wang et al. have highlighted that MSC derived CAF were able to induce an epithelial to mesenchymal transition in OCC by secreting IL-6, through the JAK2/STAT3 pathway, enhancing paclitaxel resistance [36] (see Figure 2). Surgical stress and heat shock increase secretion of IL-6 and IL-8 [37] and thus blood levels of IL-6 are increased during HIPEC in ovarian cancer [38]. As it happens, IL-6 and IL-8 are two interleukines involved in MSC's recruitment [39]. Further research should be done to investigate whether hyperthermia leads to recruitment to MSC since hyperthermia induces secretion of IL-6 and IL-8. It seems that MSC could participate to the unsatisfactory results of HIPEC sometimes observed in ovarian cancer.

ii) Immune system

Ovarian cancer is an immunogenic disease and host's immunity influences the prognostic. Indeed, ovarian tumours are invaded by immune cells: tumor-infiltrating lymphocytes. Many intermediates of the immune system thus constitute markers of survival or response to chemotherapy [40]. Fever which is by definition an increase of body temperature, is an archaic defense mechanism that increases survival against infections by mobilizing the immune system. Therefore, HIPEC may interfere with this complex system.

a. Adaptative immunity

T cells

T cells have in common the cluster of differentiation 3 (CD 3+). According to Zhang et al. there is a lymphocyte infiltration in EOC in 55% of cases. Furthermore, the 5-year survival of patients with tumor infiltrated lymphocytes (TILs) is 38% compared to 4.5% in patients whose tumors do not have TILs upon pathological examination. [41]. Among T cells, CD8+ T (cytotoxic) T cells and CD4+ T (helper) cells have also been confirmed as prognostic markers [42].

Hyperthermia leads to active recruitment of lymphocytes in veinules and lymph nodes. On the lymphocyte side, this phenomenon is mediated by L-selectin and α4β7 integrin. On the endothelial side the adhesion dependent on lymph nodes adressins (PNAd) [43] and mucosal adressin cell adhesion molecule-1 (MAdCAM-1)[44]. Moreover, as we have already seen, HIPEC and surgical stress leads to an increase of IL-6 [38] which is known to increase the expression of P-selectin and E-selectin in endothelial cells permitting adherence, tethering rolling and finally through ICAM-1, transmigration of CD8+ T cells in the tissue [45] (see Figure 2). Further research should be done to investigate whether hyperthermia increases CD8+ migration in the ovarian cancer.

Hyperthermia enhances the cytotoxic activity of CD8+ through the expression of granzyme B, perforin, and interferon γ (IFNγ) [46] and nuclear HSF promotes Fas ligand expression [47]. In a mice model, targeted inhibition of HSP 90 by novobiocin, suppressed TNF alpha production by CD4+ cells [48]. GP96 is another thermosensitive chaperone whose activation leads to priming of T cell response through a CD-91dependent manner [49]. Thus, it would be interesting to study the ability of HIPEC to potentiate CD8+'s cytotoxicity.

T cells also modulate chemoresistance in EOC. Wang et al. showed that, fibroblasts enhance the efflux of cisplatin through chelation by glutathione and that CD8+ T cells were able to alter this mechanism through secretion of IFN Gamma, suppressing the chemoresistance[50].

In total, we have shown that hyperthermia increases infiltration and cytotoxic activity of LTs. However, these lymphocytes could also be involved in fibroblast-related chemoresistance.

B cells

Although T cells are extensively explored in ovarian cancer as predictive markers and for new therapeutic ways, few studies have highlighted the importance of B cells in ovarian cancer. At histology, B cells are present within the tumoral tissue to modulate the tumor microenvironment and its immune response [51]. In ovarian cancer, it seems that low density of plasma cells CD138+ [52] and high density of naïve B cells and memory B cells combined with CD8+ T cells correlated with a better prognostic [42].

HSP are involved in B cells activation. The HSF-1 complex is functional in activated B cells only, as no hHSF-1-DNA complex can be detected in naïve B cells exposed to hyperthermia [53]. HSF-1 released HSP 90 leads to proliferation of B cells and antigen presentation [54] (see Figure 2).

But B cells also act as an immunosuppressive and pro-tumoral actor. In breast cancer, B cells reduce CD8+ activity and NK cells infiltration [55] and it has been confirmed in ovarian cancer that the presence of IL-10+ B cells of naïve B-cell phenotype was associated with less cytotoxic CD8+ T cells, allowing tumour immune tolerance [56]. In this way, the maturation of B-cells provoked by the heat shock could act as an immune boost.

b. Innate immunity

Macrophages

Monocytes are part of the circulating leukocytes; they differentiate into macrophages when they leave the circulation. They are actors of innate immunity via phagocytosis but are also antigen presenters and therefore actors of acquired immunity. Tumor associated macrophages (TAM) are the most abundant immune related stromal cells in the TME. Macrophages can differentiate in two subtypes: M2 macrophage has poor antigen-presenting capacity, prevents T-cell activation, contributes to suppressing dendritic cell (DC) functions, as well as enhances angiogenesis and metastasis. M1 macrophages are the opposite [57].

When TAMs are exposed to cisplatin, they increase their production of the chemokine CCL20 that activates its receptor CCR6 in OCC triggering EMT[58]. Facing hyperthermia, macrophages activate the HSF-1 complex. Nuclear HSF-1 promotes IL-10 and its receptor transcription in macrophages[59]. IL-10 inhibits production of many cytokines, notably IL-1, IL-6, TNF and PAF that are crucial to its anti-inflammatory activities and its amplification through different pathways (see Figure 2). Macrophage's functions are increased up to 40° and then inhibited over 41° in mice [60]. Furthermore, as we have seen previously, hyperthermia leads to vasodilatation which reduces tissue hypoxia. However, when macrophages are subjected to hypoxia, they release exosomes that deliver miR-223 to elicit a chemoresistance phenotype in EOC. HIPEC would prevent this event.

Overall, HIPEC via macrophages could have an ambivalent role: on the one hand, hyperthermia it reduces inflammatory activity via IL10 and on the other, it prevents the occurrence of chemoresistance.

Dendritic cells

Dendritic cells (DC) are highly specialized antigen presentating cells. In this manner they can recognize tumor associated antigens (TAA) and induce specific T-cell effectors. Presence of

immature DC at histology is associated with poor outcome [40]. Enhancement of DC activity or its presentation of TAA has been in the center of many trials[61].

Heat stressed EOC exosomes are able to induce dendritic cell (DC) maturation. Compared to non-heat stressed tumor exosomes, they contain more HSP 70, more MHC-1 and are more effective for inducing differentiation of activated monocytes into mature DC [62]. These DCs can induce the activation of CD4+ and CD8+ T cells to obtain an antitumor immune effect [62]. Similarly, in patients with colorectal cancer treated by local hyperthermia, exosomes derived from tumor cells are able to stimulate dendritic cells to secrete more IL-6 promoting the differentiation of Th 17 regulatory T-lymphocytes; resulting in an anti-tumor effect [63]. HSP 70 secreted by the cancer cell after chemical[64] or heat exposure [65] acts like a DC antigen enhancing immunity against the tumor through Toll Like Receptor (TLR) 4. HSP 90 also accelerates DC maturation (see Figure 2) [66].

Thus, HIPEC certainly enhances the immune activity of dendritic cells.

Natural Killer cells

Natural killer (NK) cells are cytotoxic cells that have the capacity of elicit inflammation through antigen-independent pathways and detect loss of HLA as a signal for activation. Its presence in ovarian cancer microenvironment is associated with poor prognosis [67].

Although debated, it seems that hyperthermia promotes the cytotoxicity of NK cells. HSP 70 in cancer cells increases natural killer lectin-like receptor gene 2D (NKG2D) ligand-receptors [68]. HSP 70 also stimulates NK cells through expression of NKG2D, CD56 and CD94 (see Figure 2) [69]. On the contrary, Koga et al. exposed mice to whole body hyperthermia at 42 degrees and showed less expression perforin and granzyme B but identical expression of TNF cytokines [70].

Further studies are needed to establish the exact impact of HIPEC on NK cells.

iii) Endothelial cells and microvascular tumoral network

Endothelial cells participate in tumor progression by promoting neo-angiogenesis. Anti-angiogenic therapies should therefore increase overall survival. However, these treatments are disappointing given that bevacizumab does not improve survival in ovarian cancer [71]. By blocking neo-angiogenesis, the tumor evolves in a hypoxic environment and activates alternative pathways [72].

When Sun et al. explored the variation of hypoxia after hyperthermia in various tumor, they observed that even if the main effect was increasing the oxygenation of tumoral tissue through vasodilatation, the regions with the highest hypoxia (ie lowest vascularization) indeed suffered from increased hypoxia after hyperthermia [73]. Therefore, in these areas, endothelial cells secrete angiocrines particles promoting neo-angiogenesis after hyperthermia [74,75] . This process then creates vascular niches for tumor progression [76].

Moreover, EOC is able to transform the surrounding endothelium in an angiocrine endothelium [77]. One of the ways for EOC to influence the epithelium is by secreting HSP90. Secretion of HSP 90α (one of the two the cytosolic forms) is heat inducible [78]. However it has been shown that HSP90 is increasing expression of vascular endothelial growth factors (VEGF) receptors on human endothelial and lymphatic cells (see Figure 2); and thus the possibility of decreasing this expression with an HSP 90 inhibitor [79]. In this manner, these data could represent arguments against HIPEC.

It seems mandatory to remind that endothelial cells are playing an essential role in resistance to chemotherapy. For instance, Hoarau-véchot et al, demonstrated that OCC were able to activate endothelial cells through the phosphatidylinositol 3-kinase/Akt pathway [80], when cocultured with Akt-activated endothelial cells, OCCs developed chemoresistance through Notch pathway. Therefore, even if the role of endothelial cells in hyperthermia needs

to be investigate further, it is clear that they have a real role in resistance to chemotherapy and they shouldn't be neglected.

iv) Adipose stromal cells

The peritoneal cavity contains adipose tissue. The large epiploon, which is a frequent site of metastasis, is routinely removed during debulking surgery. The peritoneum is bordered on its outer surface by adipose tissue and the mesos, the nourishing blades of the digestive tract, is mainly made up of adipose tissue. During debulking surgery, after multiple manipulations of the omentum before removal, and extended peritonectomy, adipose tissue and adipocytes are exposed to HIPEC.

In OCC, coculture with adipocytes increases chemoresistance to cisplatin and paclitaxel through the PI3K/Akt signalling pathway, arachidonic acid secretion [81], and miR21 transfer to OCC[82]. There are actually no data on the effect of HIPEC on adipose tissue.

Fever range heat exposure induces lipolysis in rat's adipocytes [83] meaning a release of free fatty acid (FFA) locally and in blood stream. However, these FFA constitute an energy reserve, contributing to tumour growth and metastasis [84].

Moreover, adipose tissue responds differently to heat depending on its location [83]. Thus, more metabolically active fat as retroperitoneal fat express more HSP after heat exposure at fever range than subcutaneal fat [83,85]. Omental fat spontaneously expresses more HSP 70, and HSP 90 [85] and cancer associated adipocytes transfers HSP 70 into their lipid droplets to facilitate FFA release[86].

Therefore, extended peritonectomy, bowel and omental manipulations could expose adipocyte to HIPEC and EOC to adipocytes and trigger a cellular alliance resulting in EOC survival within the fat.

IV- Conclusion

The intercellular mechanisms involved in the exposure of tumour microenvironment to HIPEC are various. Even if it seems that the combination of hyperthermia and chemotherapy constitutes an immune boost, it would seem that mesenchymal cells but also its endothelial and adipocyte relatives could actually protect the remaining cells and explain the peritoneal recurrences despite radical surgery supplemented by HIPEC procedure.

The tumour microenvironment constitutes a variable in tumour identity and its characterization could lead to i) better select patients beneficiating from HIPEC such as a targeted therapy. For example, high concentration of versican, a high density of T cells or low labelling in HSP 90, could constitute enhanced indications for HIPEC. ii) to use targeted therapy in addition to HIPEC: blocking resistance mechanisms involved in HIPEC, such as the use of anti-IL-6, anti CXCR-4 or anti HSP-90 during the procedure, may also be considered.

With this in mind, we are currently conducting a translational study on primary lines of advanced epithelial cancers taken during exploratory laparoscopy or debulking, in order to determine a predictive profile of response to HIPEC but also the role of different players in the microenvironment in resistance to HIPEC. Nevertheless, the study of the role of the microenvironment in the resistance mechanisms of ovarian cancer remains a topical issue of great interest.

Conflicts of interest:

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Authors' contributions:

AC and LB carried out the bibliographical research and writing.

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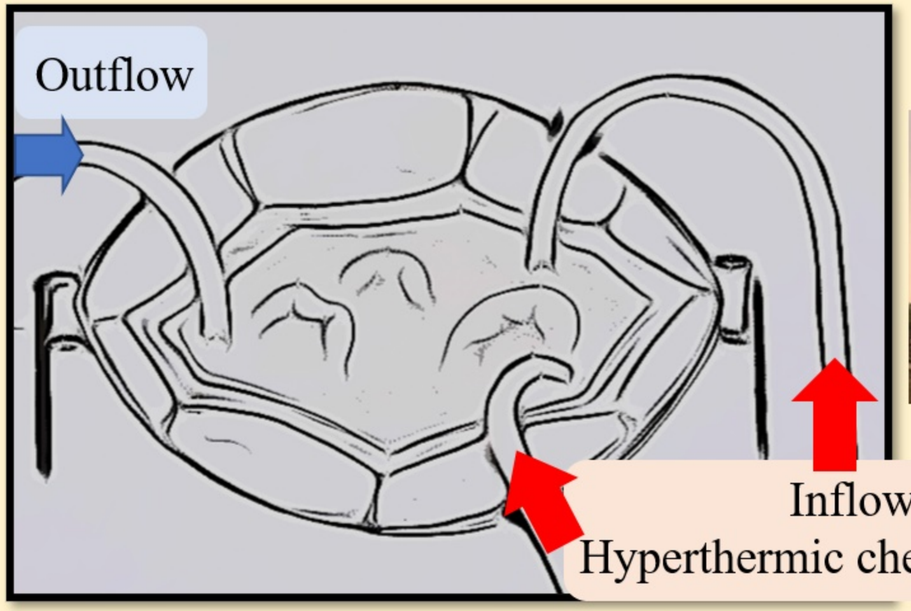
Legends:

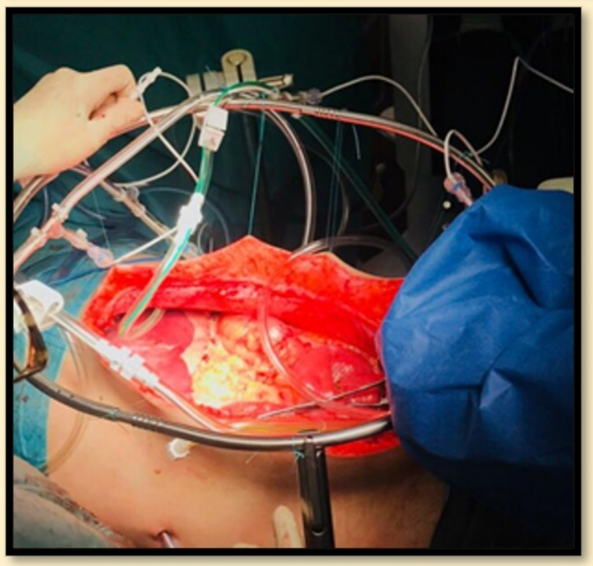
Table 1 : Table 1: HIPEC trials through the last 10 years.

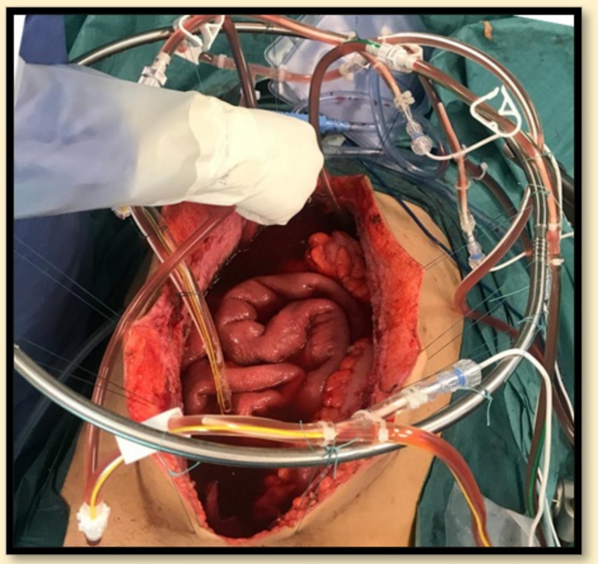
Figure 1: HIPEC open technique : Coliseum.

Figure 2: Biocellular mechanisms at work in the ovarian tumor microenvironment during HIPEC.

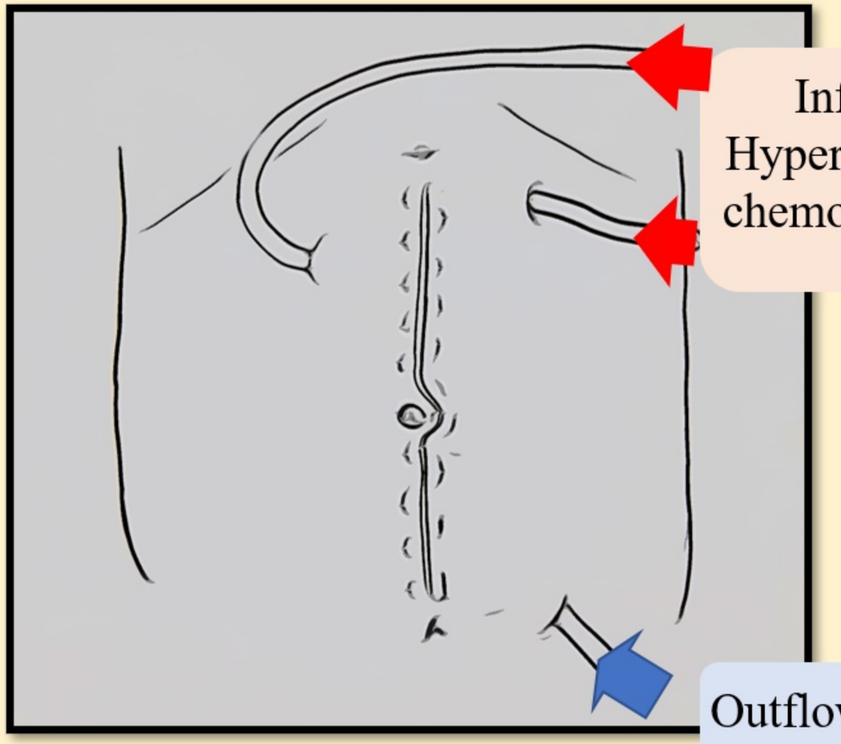
OPEN TECHNIQUE : COLISEUM



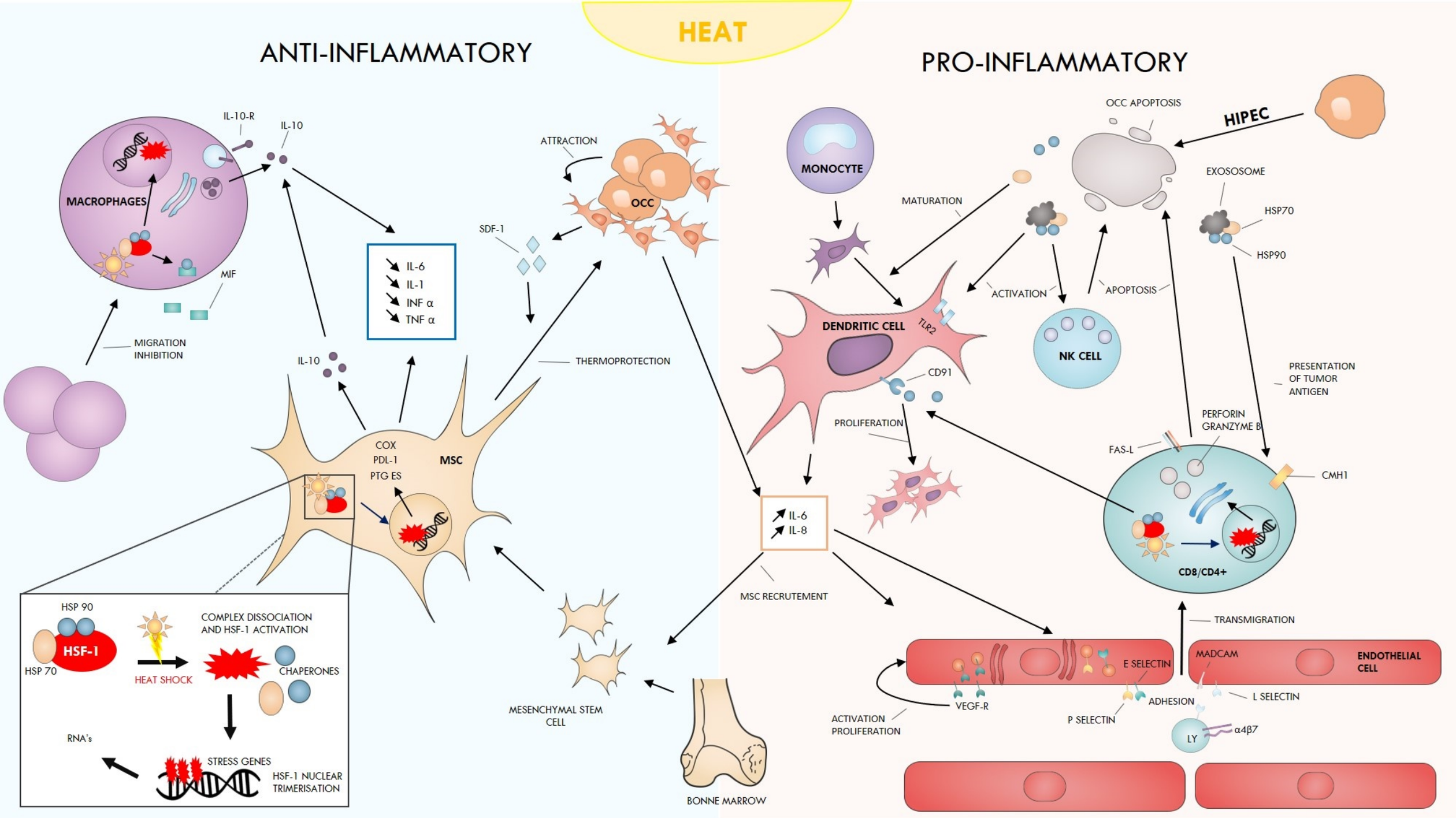




CLOSED TECHNIQUE



The OPEN technique is the most commonly used


HEAT
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PRO-INFLAMMATORY
MACROPHAGES
IL-10-R
IL-10
MIF
MIGRATION
INHIBITION
ATTRACTION
OCC
SDF-1
IL-6
IL-1
INF α
TNF α
IL-10
THERMOPROTECTION
COX
PDL-1
PTG ES
MSC
HSP 90
HSF-1
HSP 70
HEAT SHOCK
COMPLEX DISSOCIATION
AND HSF-1 ACTIVATION
CHAPERONES
RNA's
STRESS GENES
HSF-1 NUCLEAR
TRIMERISATION
MESENCHYMAL STEM
CELL
BONNE MARROW
MONOCYTE
MATURATION
OCC APOPTOSIS
HIPEC
EXOSOSOME
HSP70
HSP90
ACTIVATION
APOPTOSIS
DENDRITIC CELL
TLR2
NK CELL
CD91
PROLIFERATION
PRESENTATION
OF TUMOR
ANTIGEN
PERFORIN
GRANZYME B
FAS-L
CMH1
CD8/CD4+
IL-6
IL-8
MSC RECRUTEMENT
TRANSMIGRATION
E SELECTIN
MADCAM
ENDOTHELIAL
CELL
VEGF-R
ACTIVATION
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