REVIEW

Hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer

N. Bakrin a, b, J.M. Classe c, C. Pomel d, S. Gouy e, G. Chene a, O. Glehen b, f, *

a Service de gynécologie, hôpital Femme-Mère-Enfant, hospices civils de Lyon, 69000 Lyon, France
b EMR 3738, université Lyon-1, 69000 Lyon, France
c Centre René-Gauducheau, 44000 Nantes, France
d Centre Jean-Perrin, 63000 Clermont-Ferrand, France
e Institut Gustave-Roussy, 94085 Villejuif, France
f Service de chirurgie générale et oncologique, centre hospitalier Lyon-Sud, 165, chemin du Grand-Revoyet, 69495 Pierre-Bénite, France

KEYWORDS
Ovarian cancer; Peritoneal carcinomatosis; Hyperthermia; Hyperthermic intraperitoneal chemotherapy (HIPEC)

Summary
Ovarian cancer remains the fourth leading cause of cancer death in women in France. It is all too often diagnosed at an advanced stage with peritoneal carcinomatosis (PC), but remains confined to the peritoneal cavity throughout much of its natural history. Because of cellular selection pressure over time, most tumor recurrences eventually develop resistance to systemic platinum. Options for salvage therapy include alternative systemic chemotherapies and further cytoreductive surgery (CRS), but the prognosis remains poor. Over the past two decades, a new therapeutic approach to PC has been developed that combines CRS with hyperthermic intraperitoneal chemotherapy (HIPEC). This treatment strategy has already been shown to be effective in non-gynecologic carcinomatosis in numerous reports. There is a strong rationale for the use of HIPEC for PC of ovarian origin. On the one hand, three prospective randomized trials have demonstrated the superiority of intraperitoneal chemotherapy (without hyperthermia) in selected patients compared to systemic chemotherapy. Moreover, retrospective studies and case-control studies of HIPEC have reported encouraging survival data, especially when used to treat chemoresistant recurrence. However, HIPEC has specific morbidity and mortality; this calls for very careful selection of eligible patients by a multidisciplinary team in specialized centers. HIPEC needs to be evaluated by means of randomized trials for ovarian cancer at different developmental stages: as first line therapy, as consolidation, and for chemoresistant recurrence. Several European phase III studies are currently ongoing.

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Introduction

Epithelial ovarian cancer is the fourth leading cause of cancer death in French women after breast cancer, colorectal cancer and lung cancer. Advanced peritoneal carcinomatosis

* Corresponding author.
E-mail address: olivier.glehen@chu-lyon.fr (O. Glehen).

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HIPEC is often present at the time of diagnosis [1]. The standard therapeutic strategy for disease limited to the peritoneal cavity is a combination of cytoreductive surgery whenever possible followed by systemic chemotherapy with taxanes such as paclitaxel and platinum derivatives, with or without anti-angiogenic agents. This strategy provides complete remission in 60–80% of cases with a median survival of 35–38 months. The radicality or near-completeness of cytoreductive surgery is the main prognostic factor, as reported by a meta-analysis of 6885 patients undergoing treatment for stage III or IV ovarian cancer [2]. However, 20–30% of patients have tumor resistant to systemic cisplatin from the onset, and nearly 70% of those who respond to platinum will relapse within 5 years [3]. This interval to the development of drug resistance is defined by the time to recurrence after the first line treatment, a definition that may be questionable. Patients who relapse before the sixth month are considered chemoresistant and those who relapse after six months are considered chemosensitive [4]. The prognosis for these two groups is guarded and effective therapy with curative intent is very doubtful. Most of the clinical research in ovarian cancer is now directed toward the development of systemic treatments and targeted therapy [5]. However, the main mode of recurrence of ovarian cancer is PC and it often remains a loco-regional disease for a long time, confined to the peritoneum and intra-abdominal viscera; this makes it an ideal target for loco-regional therapy.

Rationale for hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer

The rationale for HIPEC in peritoneal carcinomatosis

Intraperitoneal delivery of chemotherapy allows exposure of the poorly vascularized tumoral tissue to high concentrations of cytotoxic agents. The blood-peritoneal barrier limits passage of these high doses into the plasma and reduces the risk of systemic toxicity [6]. Heat has a direct cytotoxic effect, and also potentiates the action of certain antimetotic agents (mitomycin C, cisplatin, oxaliplatin), as well as increasing their penetration into tumor tissue [7]. Hyperthermia also reduces the mechanisms of cellular resistance to cisplatin [8].

The results of HIPEC in primary and gastrointestinal carcinomatosis

Over the last 20 years, several teams have developed a new concept of loco-regional treatment with curative intent for peritoneal carcinomatosis: the combination of cytoreductive surgical techniques and peritoneal resection to remove all macroscopic disease [9], followed by intraperitoneal chemotherapy, particularly HIPEC, to treat microscopic or millimetric residual disease [7]. This new therapeutic modality was initially developed for the management of primary peritoneal carcinomatosis and PC of gastrointestinal origin. It is now the standard treatment for pseudomyxoma peritonei and peritoneal mesothelioma [10,11]. For PC arising from colorectal carcinoma, it is now recommended that HIPEC be performed in combination with complete cytoreduction surgery in specialized centers, based on the results of a randomized Dutch study and two registries involving more than 500 patients [12–14]. Carcinomatosis arising from gastric cancer has a poorer prognosis; HIPEC is the only technique that offers the possibility of long-term survival in very selected patients [15]. Its impact is also being evaluated for the prevention of PC from colorectal and gastric origin in the Prophyllochip and Gastrichip protocols [16].

The rationale for HIPEC in ovarian cancer

The typical natural history of ovarian carcinoma is to remain confined to the peritoneal cavity for a prolonged period and this is also the preferred site of recurrence. The effectiveness of intraperitoneal chemotherapy as first line treatment has been demonstrated in three large randomized trials [18–19]. Morbidity involving the peritoneal cavity and the complexity of the therapy have prevented its routine adoption as standard treatment despite significant improvement in median survival (49–66 months) [17,19]. HIPEC has several advantages over simple intraperitoneal chemotherapy: the administration is performed immediately following surgical debulking in an open abdomen free of adhesions, at the moment when the tumor burden is at its lowest.

As first line treatment of ovarian cancer, HIPEC has the advantage of early treatment of residual peritoneal disease, before the tumor develops a profile of acquired resistance to platinum as a result of cellular selection pressure in response to repeated courses of systemic chemotherapy. To date, HIPEC as primary treatment of ovarian cancer has not been evaluated by any study.

There are comparable theoretical benefits for HIPEC as interval therapy. However, if post-operative complications occur, they may delay or prevent the administration of the entire course of systemic chemotherapy, which is the backbone of standard therapy.

Consolidation therapy requires a second-look laparoscopy, for surgical patients who are most often deemed to be in remission by clinical, laboratory and imaging criteria. Patients with recurrent or chemoresistant ovarian carcinomas constitute a population with extremely poor prognosis. Several treatment modalities have been proposed such as 2nd line cytoreductive surgery, 2nd line chemotherapy, higher dose chemotherapy, intraperitoneal chemotherapy, radiotherapy, immunotherapy, and hormone therapy. But none of these therapeutic modalities has been proven to be effective. However, since the natural history of ovarian cancer is to remain confined to the peritoneal cavity and intra-abdominal viscera, this is the ideal target for loco-regional treatment.

Conditions necessary for performing CRS with HIPEC

Cytoreductive surgery in peritoneal carcinomatosis aims to resect all macroscopic disease but inevitably leaves microscopic disease in place. Intraperitoneal chemotherapy, particularly HIPEC, then plays the role of completing CRS by eradicating the residual microscopic disease. Intraperitoneal chemotherapy agents under hyperthermic conditions penetrate tissue only to a depth of 2 to 3 mm [20]. Combined CRS/HIPEC should not be proposed unless optimal debulking can be achieved leaving residual tumor studding of less than 1–2 mm thickness.

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Principles and technical modalities for CRS and HIPEC

The first use of HIPEC in humans was described by Spratt et al. in 1980 to treat a patient with pseudomyxoma peritonei. It was largely developed in Japan during the 1980s, along with techniques of cytoreduction for the treatment of PC originating from gastric cancer [21]. Thereafter, the techniques and management strategies of HIPEC and CRS were refined in France and Europe, Asia and North America by surgical pioneers such as Gilly [22], Elias [23], Yonemura and Sugarbaker [24]. Several techniques of HIPEC have been described [7,23], but no single technique has so far demonstrated its superiority. Nevertheless, since its effectiveness has been validated by prospective trials, there is a need for standardization of practices. The technical particularities of HIPEC include the instillation circuit, the timing of parietal closure (before or after HIPEC), the duration of treatment, target temperatures, and the choice and dosage of antimitotic agents.

Antimitotic agents

The rationale for the choice of a particular chemotherapy agent is based on its clinical efficacy and the pharmacokinetics in the peritoneal cavity. The ideal agent must have a high molecular weight that limits passage across the peritoneovenous barrier, a high level of plasma clearance, and a mode of action that is potentiated by hyperthermia [25]. Cisplatin is the most widely used chemotherapy agent for treatment of PC of ovarian origin [26–31]. Other agents (oxaliplatin, paclitaxel, doxorubicin, carboplatin, irinotecan, gemcitabine) have also been tested [7,13,20].

However, with the exception of cisplatin and mitomycin C, few therapeutic protocols have been validated by phase II–III studies and no standard dose has yet been defined. However, the pharmacokinetics of cisplatin depend on many parameters such as the solute concentration, the volume and the type of solution used, the duration of instillation, and the temperature [5]. In a recent phase I dose-escalation study that evaluated HIPEC with cisplatin as 1st line treatment of initially unresectable ovarian cancers, the dose of 70 mg/m² for 1 hour at 42 °C was found to be the recommended protocol [32].

Morbidity and mortality of HIPEC

HIPEC’s toxicity when combined with CRS is manifested largely as surgical complications (anastomotic leakage, intraperitoneal septic complications, bleeding). Complications specific to HIPEC are mainly hematologic, as well as the risk of kidney failure related to the predominant use of cisplatin. The heterogeneity of the various series (population consisting of primary, recurrent, and/or chemoresistant ovarian carcinoma without subgroup analysis), the multiplicity of protocols and associated surgical procedures, and the different ways of presenting results and analysis make comparison of data difficult. However, the rates of morbidity and mortality for HIPEC in the treatment of ovarian cancer are found to be generally lower than those found for the treatment of primary and gastrointestinal PC and are very similar to those reported by Bristow et al. with CRS alone for the surgical treatment of peritoneal recurrence [33].

Post-operative mortality

In published series on the use of HIPEC for PC of ovarian origin, post-operative mortality ranges from 0–10% (Table 1). Post-operative mortality was 0.8% in the French registry of HIPEC on 566 patients [40], while it was 4.1% for patients with PC of non-gynecologic origin who underwent the same combination therapy. Mortality in a review of the largest international series was 3% [41,42].

Post-operative morbidity

In the series of patients treated with HIPEC for PC of ovarian origin, the incidence of grade 3–4 morbidity varies from 0 to 32% (Table 1), versus 29–40% primary and gastrointestinal PC [41,42]. Surgical morbidity consisted mainly of anastomotic leak, gastrointestinal perforation, intraperitoneal hemorrhage, and evisceration. In multivariate analyses of the largest reported series, several independent risk factors for morbidity have been identified: the extensiveness of carcinomatosis, the radicality of cytoreductive surgery, the duration of the total procedure, the extent of peritoneal resection, and the number of anastomoses [40–42]. Lower mortality and morbidity was reported for HIPEC treatment of PC of ovarian origin; this can be explained by the lesser extent of CRS and fewer intestinal resections and anastomoses; in addition, these patients have often benefited from downstaging of their carcinomatosis due to effective systemic chemotherapy.

The specific morbidity of HIPEC is linked to passage of the chemotherapy into the systemic circulation resulting in hematologic toxicity; grade 3–4 morbidity occurs in 8–31% of cases, particularly in patients whose bone marrow has already been impaired by multiple cycles of systemic chemotherapy using agents similar to those used for HIPEC. This specific morbidity is also linked to the type of chemotherapeutic agent used. The use of oxaliplatin increases the risk of bleeding complications. The CHIPOVAC study, a prospective trial to evaluate HIPEC for consolidation treatment, was suspended after enrollment of 31 patients because nine cases of post-operative hemoperitoneum occurred requiring at least one re-operation [43]. The use of cisplatin is associated with a risk of kidney failure that requires optimal peri-operative hydration. In the French registry [40], 8% of patients developed post-operative renal failure, which became chronic in 2% and dialysis-dependent in 1%. Prevention of cisplatin nephrotoxicity may also be aided by the use of amifostine, an inorganic triphosphate with a thiol radical that helps to selectively reduce the toxicity of cisplatin in normal tissue without impairing its anti-cancer properties [44].

Quality of life

Quality of life can be evaluated objectively using self-administered patient questionnaires at repeated intervals throughout the therapeutic course and convalescence. Unlike primary and gastrointestinal PC where HIPEC is the only possible treatment, ovarian cancer remains susceptible to systemic chemotherapy for a prolonged time, although this also causes constraints and uncomfortable side effects (hair loss, peripheral neuropathy, anorexia). Preservation or improvement of the patient’s quality of life during HIPEC treatment must be a constant concern for the surgeon. Several recent prospective studies that evaluated CRS and
HIPEC found that the quality of life was preserved by this type of procedure [45,46]. Surgery should be macroscopically complete (the sine qua non for prolonged survival) and should preserve digestive and urinary comfort that is necessary for a normal social life. Extensive intestinal resections that impair digestion and nutrition requiring permanent parenteral nutrition (extensive enterectomy with or without total gastrectomy or colectomy) should not be performed. Posterior pelvic exenteration is often necessary, however, the vesical trigone must be left intact because, in this context, total cystectomy should never be performed.

**Survival**

The studies that have evaluated combined CRS-HIPEC in the treatment of recurrent or chemoresistant ovarian carcinomas have mostly been phase I–II studies with low numbers of patients. Study populations are heterogeneous and include patients with advanced and sometimes uncontrolled disease. They include patients treated as 1st line therapy, consolidation therapy, or after recurrence. The carcinologic results are expressed according to a variety of criteria (median or mean overall survival, survival at 1, 3, or 5 years) and multiple HIPEC protocols have been used, which makes the comparison of these series difficult.

**First line or consolidation therapy**

Standard 1st line treatment demands complete cytoreductive surgery along with adjuvant or peri-operative chemotherapy using carboplatin and taxol, delivered either systemically or intraperitoneally [47]. Anti-angiogenic agents may also be used. The radicality of cytoreduction is the main independent prognostic factor. Other prognostic factors such as the extentiveness of PC as evaluated by the Sugarbaker’s Peritoneal Cancer Index (PCI) or the chemoresistance to platinum are also fundamental prognostic factors [40,48]. However, there is great variation in the criteria for inclusion of patients in various trials of standard 1st line HIPEC treatment; this makes comparisons very difficult. Comparative results are summarized in Table 2. The number of patients in series that evaluated 1st line HIPEC therapy are usually quite limited but reported median survival in selected patients are superior to those obtained with standard systemic chemotherapy. The survival results of the French registry are lower, but this series included patients who were refractory or resistant to 1st line treatment and thus have poorer prognosis. A Dutch randomized trial (OVHIPEC) that studied interval HIPEC among patients who were initially unresectable should provide a more objective assessment of the contribution of HIPEC in 1st line treatment.

**HIPEC for recurrent disease**

No standard treatment is clearly established for patients with recurrence after 1st line treatment, whether of good or poor quality. Most patients with such recurrences are currently treated with new combinations of systemic chemotherapy. A repeat laparotomy with complete cytoresection is also an option that several authors have used to obtain median survival of over 30 months [33,54,55]. But again the comparisons between series evaluating HIPEC in this context are difficult for the same problematic variation of selection criteria (Table 3). For example, in the DESKTOP I study [55], the median survival of patients operated on for recurrence was 29.5 months, but the median survival was only 20 months for patients with PC, who make up the bulk of patients in HIPEC series. For recurrent disease, the extentiveness of carcinomatosis (as assessed by the PCI), chemoresistance (particularly platinum resistance), and the completeness of CRS have major prognostic impact [28,40]. Performing HIPEC after a CRS that leaves supra-millimeter residual disease is ineffective or weakly effective [57]. However, the results of CRS-HIPEC for recurrence appear even more promising than for 1st line treatment. Three case-control studies [58–60] have compared combined systemic chemotherapy and CRS alone versus identical treatment plus HIPEC in patients with recurrent disease; they showed significantly improved results with the addition of HIPEC (Table 4). In the French registry that included 474 patients with recurrence and PC [40], the median survival was 52 months for platinum-resistant patients and 47 months for platinum-sensitive patients. The combination of rigorous CRS with HIPEC treatment to eradicate any residual disease that inevitably leads to recurrence is a very tempting option, but the results must be validated in further phase III studies.

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The CHIPOR study (PHRC 2010), which opened in April 2011, is designed to evaluate the effectiveness of HIPEC as treatment of the first recurrence of ovarian cancer in patients with platinum-sensitive ovarian cancer.

Conclusion

HIPEC associated with complete CRS yields encouraging survival results in patients treated for PC of ovarian origin, whether as 1st line therapy for advanced disease or for recurrent disease. Post-operative morbidity and mortality are lower than those found with CRS-HIPEC treatment of primary and gastrointestinal PC in terms of expected benefit at an acceptable risk. The main criteria for patient selection depend on the possibility of effective cytoreductive surgery and the extensiveness of carcinomatosis (PCI), which are the main prognostic factors. The eligibility of patients for this type of treatment requires rigorous selection, and management should be carried out by well-trained multidisciplinary teams (surgeons, gynecologists, anesthetists, medical oncologists, radiologists and pathologists) practicing in a specialized center. Finally, the demonstration of the potential benefit of HIPEC must be validated by ongoing and future randomized trials.

HIGHLIGHTS

• The peritoneal cavity is the preferred site for local extension and for relapse of ovarian cancer, and therefore the ideal theoretical target for loco-regional treatment (CRS plus HIPEC).

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Table 2 Survival results for first line HIPEC treatment for advanced ovarian cancers.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Number of patients</th>
<th>Chemotherapy</th>
<th>Cytoreduction</th>
<th>Median survival (months)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vergote et al. [49]</td>
<td>2010</td>
<td>334</td>
<td>Neoadjuvant IV</td>
<td>&lt;1 cm</td>
<td>30</td>
<td>49%</td>
</tr>
<tr>
<td>Eisenkop et al. [50]</td>
<td>2003</td>
<td>408</td>
<td>IV</td>
<td>&lt;1 mm</td>
<td>58</td>
<td>47%</td>
</tr>
<tr>
<td>Chi et al. [51]</td>
<td>2009</td>
<td>408</td>
<td>IV</td>
<td>&lt;1 mm</td>
<td>54</td>
<td>47%</td>
</tr>
<tr>
<td>Armstrong et al. [18]</td>
<td>2006</td>
<td>214</td>
<td>IP</td>
<td>&lt;1 cm</td>
<td>66</td>
<td>29%</td>
</tr>
<tr>
<td>Helm et al. [52]</td>
<td>2010</td>
<td>20</td>
<td>HIPEC</td>
<td>&lt;1 cm</td>
<td>58</td>
<td>67%</td>
</tr>
<tr>
<td>Pomel et al. [36]</td>
<td>2010</td>
<td>31</td>
<td>HIPEC</td>
<td>&lt;1 mm</td>
<td>NR</td>
<td>61%</td>
</tr>
<tr>
<td>Deraco et al. [27]</td>
<td>2011</td>
<td>26</td>
<td>HIPEC</td>
<td>&lt;1 mm</td>
<td>NR</td>
<td>61%</td>
</tr>
<tr>
<td>Bakrin et al. [40]</td>
<td>2013</td>
<td>92</td>
<td>HIPEC</td>
<td>&lt;1 mm</td>
<td>42</td>
<td>17%</td>
</tr>
<tr>
<td>Gonzalez-Bayon et al. [53]</td>
<td>2013</td>
<td>15</td>
<td>HIPEC</td>
<td>&lt;1 mm</td>
<td>78</td>
<td>72%</td>
</tr>
</tbody>
</table>

IV: intravenous; IP: intraperitoneal; HIPEC: hyperthermic intraperitoneal chemotherapy; NR: not reported.

Table 3 Survival results for HIPEC treatment for recurrent ovarian cancer.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Quality of cytoreduction</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanon et al. [26]</td>
<td>2004</td>
<td>23</td>
<td>CRS and HIPEC</td>
<td>Complete</td>
<td>38</td>
</tr>
<tr>
<td>Harter et al. [55]</td>
<td>2006</td>
<td>170</td>
<td>CRS</td>
<td>Complete</td>
<td>45</td>
</tr>
<tr>
<td>Benedetti Panici et al. [54]</td>
<td>2007</td>
<td>37</td>
<td>CRS</td>
<td>Complete</td>
<td>21</td>
</tr>
<tr>
<td>Oksefjell et al. [56]</td>
<td>2009</td>
<td>68</td>
<td>CRS</td>
<td>Complete</td>
<td>16</td>
</tr>
<tr>
<td>Helm et al. [52]</td>
<td>2010</td>
<td>83</td>
<td>CRS and HIPEC</td>
<td>—</td>
<td>30</td>
</tr>
<tr>
<td>Bakrin et al. [40]</td>
<td>2013</td>
<td>356</td>
<td>CRS and HIPEC</td>
<td>Complete</td>
<td>52</td>
</tr>
</tbody>
</table>

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy.

Table 4 Case-control studies that compared CRS combined with HIPEC versus CRS alone for recurrent ovarian cancer.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Survival for CRS + HIPEC</th>
<th>Survival for CRS alone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munoz-Casares et al. [59]</td>
<td>26</td>
<td>58% at 5 years</td>
<td>17% at 5 years</td>
<td>0.046</td>
</tr>
<tr>
<td>Spiliotis et al. [58]</td>
<td>48</td>
<td>50% at 3 years</td>
<td>18% at 3 years</td>
<td>0.01</td>
</tr>
<tr>
<td>Fagotti et al. [60]</td>
<td>67</td>
<td>68% at 5 years</td>
<td>42% at 5 years</td>
<td>0.017</td>
</tr>
</tbody>
</table>

The peritoneal cavity is the preferred site for local extension and for relapse of ovarian cancer, and therefore the ideal theoretical target for loco-regional treatment (CRS plus HIPEC).
• The morbidity and mortality results of CRS with HIPEC are comparable to those for CRS alone.
• The selection of eligible patients must be rigorous and management should be provided by a multidisciplinary team in a specialized center.
• The Peritoneal Cancer Index developed by Sugarbaker is a major prognostic factor for all cases of carcinomatosis, and should be used in the selection of therapeutic indications.
• The survival results reported by retrospective case-control studies are particularly promising, especially for chemoresistant disease.
• Several Phase III trials are currently underway to assess the actual role of HIPEC in the management of ovarian cancer at various stages (first-line, consolidation, recurrence).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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