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REVIEW ARTICLE

Is it the right moment to include hyperthermic intraperitoneal chemotherapy as standard in ovarian cancer management? A reappraisal

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Summary

Ovarian cancer is a leading cause of cancer-related death in women and often is diagnosed at an advanced stage with diffuse peritoneal carcinomatosis. Since it is mainly confined to the peritoneal cavity, even after recurrence, it is an ideal target for loco-regional therapy. The standard therapeutic strategy of advanced ovarian cancer is cytoreductive surgery followed by systemic chemotherapy. Intraperitoneal chemotherapy used as adjuvant therapy has shown a survival benefit in ovarian cancer. Hyperthermic intraperitoneal chemotherapy (HIPEC) has several advantages over simple intraperitoneal chemotherapy. This has prompted the use of cytoreductive surgery (CRS) followed by HIPEC in the management of ovarian cancer as a part of first and second line treatment for recurrent disease.

Key words: *HIPEC, hyperthermic intraperitoneal chemotherapy, ovarian cancer*

Introduction

Ovarian cancer accounts for 239,000 new cancer cases worldwide and it is the leading cause of cancer related death among gynecological malignancies, with 152,000 deaths attributed to the disease each year [1]. The vast majority of the patients are diagnosed in stages III and IV and often advanced peritoneal carcinomatosis is present at the time of diagnosis [2].

The standard therapeutic strategy for advanced ovarian cancer is cytoreductive surgery (CRS) followed by adjuvant systemic chemotherapy consisting of carboplatin, paclitaxel and bevacizumab in many treatment protocols [3-5].

The result of this approach is complete remission in 60-80% of the cases with a median survival of 35-38 months. Even though most of the patients have a very good initial response, there is still a great number of patients that recur with the majority of the recurrences located in the peritoneum. Most of the times after recurrence, the disease remains confined to the peritoneal cavity for a long time consisting an ideal target for loco-regional therapy [6]. This is attributed to the propensity of ovarian cancer cells to selectively invade the mesothelium of the peritoneal surface, forming micro-metastases whitch are only supplied by dif-

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fusion until they reach a size of 1 mm^2 [7,8]. Due to lack of vascularization, it is likely that micrometastases and free-floating cancer cells cannot be eliminated adequately by either surgery or systemic chemotherapy.

This therapeutic gap is attempted to be filled by intraperitoneal (IP) treatment modalities, including Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

The rationale of HIPEC in ovarian cancer

Since ovarian cancer tends to remain confined to the peritoneal cavity, there is a strong rationale for using intraperitoneal chemotherapy. Using chemotherapy in the peritoneal cavity allows exposure of the poorly vascularized tumor tissue to high concentrations of cytotoxic drugs. This exposure is accompanied by limited systemic toxicity as the peritoneal surface serves as a barrier between the peritoneal compartment and the blood vessels, as Dedrick et al. hypothesized in 1978 [9].

This hypothesis was the beginning for the introduction of modern IP treatments. Two large randomized trials have shown the effectiveness of intraperitoneal chemotherapy even as first-line treatment [10,11]. Armstrong et al. [11] demonstrated that the median duration of overall survival in the intravenous therapy and intraperitoneal therapy groups was 49.7 and 65.6 months, respectively. Alberts et al. [10] concluded that as compared with intravenous cisplatin administration, intraperitoneal cisplatin significantly improved survival, while significantly fewer toxic effects in patients with stage III ovarian cancer and residual tumor masses of 2 cm or less were noted.

HIPEC has the additional advantage of heat usage which has several theoretical benefits. Heat has not only a direct cytotoxic effect, but it augments the action of certain chemotherapeutic agents (mitomycin C, cisplatin, oxaliplatin) and also increases their penetration into tumor tissue. In addition, hyperthermia increases the cellular sensitivity to cisplatin [12].

Furthermore, HIPEC is applied right after the surgical debulking in an abdomen which is open and free of adhesions. Moreover, the cytoreduction has been already performed and this is the moment when the tumor burden is at its nadir. This allows for the direct delivery of chemotherapy at the site of disease and therefore a homogeneous distribution can be achieved with the use of HIPEC.

Additionally, using HIPEC as first-line treatment for ovarian cancer has the advantage of early treatment of residual peritoneal disease before the development of acquired resistance to platinum as a result of cellular selection process in response to repeated courses of systemic chemotherapy.

Principles and technical modalities for CRS and HIPEC

Even though there are several techniques of HIPEC, none of them has so far proved to be superior in comparison to the others [12]. The technical characteristics of HIPEC include the instillation circuit, the timing of peritoneal closure (before or after HIPEC), duration of treatment, target temperatures and the choice/dosage of antimitotic agents. The ideal antimitotic drug should have a high molecular weight in order not to cross the peritoneo-venous barrier, increased level of plasma clearance, and a mode of action that is augmented by hyperthermia [13]. Cisplatin is the most widely used chemotherapeutic agent for the treatment of peritoneal carcinomatosis of ovarian origin [14-16]. Other agents (oxaliplatin, paclitaxel, doxorubicin, carboplatin, irinotecan, gemcitabine) have also been tested.

Morbidity and mortality of CRS and HIPEC in ovarian cancer

Surgical complications from the use of HIPEC when combined with CRS are mainly anastomotic leakage, bowel perforation, intraperitoneal hemorrhage and wound dehiscence. Also, hematologic complications and renal failure related to cisplatin are reported in the literature [17].

It is very interesting that in the available different series the variability of patient population, such as primary recurrent and /or chemo-resistant ovarian carcinoma, the different protocols and surgical procedures that have been applied make the interpretation of data very difficult.

It has been demonstrated that morbidity and mortality rates from the use of HIPEC in the treatment of ovarian cancer are lower than those reported for the treatment of primary and gastrointestinal peritoneal carcinomatosis [6].

In addition, the numbers seem to be equal to those presented when using CRS alone for the surgical treatment of peritoneal recurrence [18].

HIPEC in the management of ovarian cancer

First-line or consolidation therapy

Currently, first-line line treatment for ovarian cancer consists of debulking surgery along with chemotherapy either adjuvantly or peri-operatively using cisplatin and taxanes. These can be delivered

either systemically or intraperitoneally [19]. In addition, anti-angiogenic agents may also be used [5]. In peritoneal carcinomatosis the surgeon's target is the resection of all the macroscopic disease but inevitably there is microscopic disease left in place. The main independent prognostic factor is the completeness of the cytoreduction. The major advantage of intraperitoneal chemotherapy, and in particular HIPEC, is that it complements CRS by eliminating the residual microscopic disease. It is known that chemotherapeutic agents when used in the peritoneal cavity under hyperthermic conditions can penetrate tissue only to a depth of 2 to 3 mm [20]. The combination of CRS/HIPEC should not be proposed unless optimal cytoreduction is achieved with residual tumor less than 1-2 mm thickness. Even though there are limited data regarding the use of HIPEC as first-line treatment, there are reports showing clearly that the survival rate is higher in comparison to standard systemic chemotherapy [11,17,21-26].

Recently three randomized trials using HIPEC in the first-line setting were presented [27-29].The first study [27] enrolled patients who underwent either primary or interval debulking surgery and patients who were randomized to continue after cytoreduction with HIPEC or not. No statistically significant improvement was noted in the overall survival in the the study population. However, a trend favoring HIPEC in the overall survival of the subgroup of patients subjected to interval debulking was noted but further follow up is needed.

The benefit from HIPEC in patients treated with neoadjuvant chemotherapy and interval debulking surgery was confirmed by another randomized phase III trial [28]. In this study addition of HIPEC to standard treatment improved both recurrence free and overall survival in stage III ovarian cancer patients.

The third study [28] investigated whether the addition of HIPEC to interval cytoreductive surgery would improve outcomes among patients who were receiving neoadjuvant chemotherapy for stage III epithelial ovarian cancer and the conclusion was that the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects.

HIPEC for recurrent disease

The use of CRS-HIPEC for the ovarian recurrent disease seems to have even more promising outcome than the results when used for first-line treatment. There are three case-control studies [30-32], that compared combined systemic chemotherapy and CRS alone versus the same treatment plus HIPEC in patients with recurrence; they all showed a significant benefit favouring HIPEC. The most important prognostic factors in recurrence is the extent of disease (according to peritoneal carcinomatosis index (PCI)), the platinum-resistance disease and the completeness of CRS) [14,22]. When HIPEC is used after CRS, that has already resulted in supra-millimetric residual disease, it is ineffective or weakly effective [33]. We should highlight the CHIPOR study (PHRC 2010) [34], which opened in April 2011. It is designed to assess the efficacy of HIPEC when used for the first recurrence of ovarian cancer in patients with platinum-sensitive ovarian cancer.

There is a single-institution randomized phase III trial by Spiliotis et al. which compares the standard cytoreduction in first recurrence with cytoreduction plus HIPEC (with cisplatin, 100 mg/m^2, and paclitaxel, 175 mg/m^2, in platinum-sensitive disease; and doxorubicin, 35 mg/m^2, and paclitaxel, 175 mg/m^2, or mitomycin, 15 mg/m^2, in platinum-resistant disease) [35]. A significant improvement was found in the mean overall survival (OS): 29.7 months in patients that HIPEC had been performed in contrast to 13.4 months in patients that underwent only surgery. It is important to mention, that platinum-resistant patients had a significant improvement in median OS, but they still had a significantly decreased OS compared with the OS seen in patients with platinum-sensitive disease. As expected, the highest OS was found in patients that undrewent a complete debulking and received HIPEC; also, the PCI score that shows the remaining disease was an independent prognostic factor. When PCI score was above 15, OS was significantly lower.

On the other hand, there are several weaknesses in the presentation of the data that undermines the validity of this first randomized HIPEC trial: There is no information on PFS, the authors do not provide median follow-up data, and the Kaplan-Meier survival curve shows a high number of censored cases.

Also, there is no information related to the postoperative first-line treatment and the complication rates. Moreover, different regimens were used in patients with the platinum-sensitive and platinum-resistant disease.

Currently, there are ongoing randomized trials [29,34,36] evaluating the efficacy of HIPEC in ovarian cancer. These studies will certainly provide more useful information about this treatment modality.

The future outlook

Although there is a strong rationale for the implementation of HIPEC in ovarian cancer treatment, scientifically sound data from randomized

clinical trials are lacking. Recently, DESKTOP III [37] confirmed the role of optimal cytoreduction in the recurrent disease, highlighting that patients gained the maximal benefit from the complete resection of all visible lesions both at the frontline and the recurrence setting. We reached the same conclusion by the HIPEC trials as well, since the result of HIPEC is related to PCI, therefore the possibility to achieve optimal cytoreduction. Based on the available data two major questions emerge for further research and clinical application regarding HIPEC: a) when is the best setting to perform HIPEC at frontline treatment or at recurrence; and b) is it high time for the inclusion of HIPEC in standard clinical practice?

Although optimal cytoreduction accompanied with HIPEC offered the greater OS in the single phase III trial [34], there are no data regarding the interaction of HIPEC with the surgical completeness. In addition, two recent randomized trials [28,29] demonstrated that the patients subjected to interval cytoreduction may enjoy the greatest benefit from this technique. This could be explained by the very good prognosis of patients with complete cytoreduction both at frontline and the recurrence setting.

Furthermore, it is known that the percentage of optimal cytoreduction achieved at interval debulking is much higher than that at primary one.

In addition, the only phase III randomized trial [34] with the use of HIPEC has been performed in recurrent patients and perhaps this is the setting where a still experimental technique should be primarily tested and applied. However, recent data from randomized trials in the frontline setting suggests that there is a possible benefit from HIPEC in the upfront treatment of patients that receive neoadjuvant chemotherapy and interval cytoreduction.

Therefore, more data is required in order to endorse HIPEC as an approved treatment in ovarian cancer. Up to then, HIPEC could be considered as a part of clinical trials in the initial treatment of patients with residual disease and those with recurrent disease that fulfill the criteria in order to be subjected to secondary debulking surgery.

Conclusion

The rationale for HIPEC as part of a multimodal treatment in patients with advanced ovarian cancer is strong. In combination with CRS, this form of aggressive loco-regional therapy has the potential to cure patients, given that hyperthermia enhances tumor penetration and the cytotoxic effects of chemotherapy. HIPEC does not increase significantly morbidity and mortality compared to CRS alone. The main criteria for patient selection depend on the possibility of effective cytoreductive surgery and the extend of carcinomatosis (PCI score), which are the main prognostic factors. This type of treatment should be offered at experienced centers by well-trained multidisciplinary teams (surgeons, gynecologic oncologists, anesthetists, medical oncologists, radiologists and pathologists) after meticulous patient selection.

Conflict of interests

The authors declare no conflict of interests.

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